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PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 21 December 1999 (21.12.99)	
International application No. PCT/SE99/00511	**Applicant's or agent's file reference** PM 445 PC
International filing date (day/month/year) 30 March 1999 (30.03.99)	**Priority date** (day/month/year) 31 March 1998 (31.03.98)
Applicant PERSSON, Bertil et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

27 October 1999 (27.10.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer A. Karkachi
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992) 3023815

U 012894-7

PATENT COOPERATION TREATY

WO 99/52589
PCT/SE99/00511

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
MAGNUSSON, Gustav
Magnupatent AB
P.O. Box 6207
S-200 11 Malmö
SUÈDE

Date of mailing (day/month/year)	
21 October 1999 (21.10.99)	
Applicant's or agent's file reference PM 445 PC	**IMPORTANT NOTICE**
International application No. PCT/SE99/00511	**International filing date** (day/month/year) 30 March 1999 (30.03.99)
Priority date (day/month/year) 31 March 1998 (31.03.98)	
Applicant ADITUS MEDICAL AB et al	

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,CN,EP,IL,JP,KP,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CU,CZ,DE,DK,EA,EE,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,UA,UG,UZ,VN,YU,ZA,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   21 October 1999 (21.10.99) under No. WO 99/52589

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

Telephone No. (41-22) 338.83.38

3762

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

3700

09/601751

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PM 445 PC		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE99/00511	30.03.1999	31.03.1998
International Patent Classification (IPC) or national classification and IPC7		
A 61 N 1/30, A 61 B 5/05		
Applicant		
Aditus Medical AB et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
27.10.1999	22.06.2000
Name and mailing address of the IPEA/SE	Authorized officer
Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. 08-667 72 88 Telex 17978 PATOREG-S	Nikolaj Hautaviita/AE Telephone No. 08-782 25 00

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE99/00511

I. Basis of the report

1. This report has been drawn on the basis of *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

☐ the international application as originally filed.

☒ the description, pages 1-21, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____.

☒ the claims, Nos. 9-18, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. 1-8, filed with the letter of 18.04.2000,
Nos. _____, filed with the letter of _____.

☒ the drawings, ~~sheets~~/fig 1-12, as originally filed,
~~sheets~~/fig _____, filed with the demand
~~sheets~~/fig _____, filed with the letter of _____,
~~sheets~~/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, ~~sheets~~/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE99/00511

III. Non-establishment f opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 4

because:

☐ the said international application, or the said claims Nos. _____
relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____
are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed.

☒ no international search report has been establised for said claims Nos. 4

V. Resoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-3,5-18	YES
	Claims		NO
Inventive step (IS)	Claims	1-3,5-18	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-3,5-18	YES
	Claims		NO

2. Citations and explanations

The aim of the claimed invention is to make electrodynamic treatment of tumors more efficient especially with internal organs. This is achieved by measuring the impedance in the tissue under treatment. The size of the impedance controls the size of the pulse by a feedback coupling. The electrodes are designed in that way that the field lines can be focused to the desired treatment region.

The following documents were cited in the International Search Report:

D1 WO 97/07853, A
D2 WO 93/23112, A1
D3 US 5,527,357, A

D1 describes a device for distributing medical substances to an organ with the aid from a pulsed electrical field. The impedance is measured and used, by feedback coupling, to control the size of the pulse.

D2 describes a medical device with pointed electrodes. The electrodes are surrounded with the insulating layer of an electrode plate.

D3 describes a device shaped like a mask used to apply electrical current to acupuncture points.

The invention differs from prior art in that internal organs are treated. Prior art inventions can not be used to treat internal organs. It is not considered obvious to a person skilled in the art to use the devices in prior art for treatment of internal organs. Thus, the invention involves an inventive step.

.../...

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: BOX V.

Accordingly, the claimed invention, claims 1-3, 5-18 fulfills the requirement of novelty (N), the requirement of inventive steps (IS), and the requirement of industrial applicability (IA).

CLAIMS PCT/SE99/00511

1. An apparatus (60) for controlling the size of, configuration of and/or duration of electric fields which are generated by a voltage generator (1) between electrodes (6,15,16,24) included in the apparatus or between electrodes (6,15,16,24) connected to the apparatus where the apparatus includes means (4,5) for distributing the voltage pulses to the electrodes (6,15,16,24) for the formation of the electric fields, and where the electrodes are designed to be secured at a restricted region of a human or an animal or are designed to be inserted in said region, c h a r a c t e r i z e d in that said region excludes the skin of a human or an animal, that an impedance measurement unit (50) included in the apparatus is disposed, on treatment of tissue or organs adjacent or in said region, to determine the impedance and/or resistance between said electrodes; and that a control and converter unit (10) is included in the apparatus or is connected thereto in order, prior to each voltage pulse or chain of voltage pulses and based on the measurement impedance and/or resistance, to control the size of, number of, configuration of and/or duration of the voltages applied to the electrodes.

2. The apparatus as claimed in Claim 1, c h a r a c t e r i z e d in that the control and converter unit (10) includes a VDU (10a); that the control and converter unit is disposed, prior to the start of the generation by the voltage generator (1) of a pulse or chain of pulses, to show on the VDU (10a) the form of the pulse or chain of pulses calculated by the control and converter unit; and that means are included in said control and converter unit for manual or automatic acceptance of said calculated formation.

3. The apparatus as claimed in Claim 1 or 2, c h a r a c t e r - i z e d in that the electrodes (6,15,16,24) are common for the impedance measurement unit (50) and for said means (4,5) for emitting voltage pulses; or that separate electrodes (4,5) are provided for the impedance measurement unit and said means for emitting voltage pulses.

4. The apparatus as claimed in any of the preceding Claims, c h a r a c t e r i z e d in that the electrodes (6,15,16,24) are disposed, to be placed in a restricted region in a human or in an animal or in positions entailing that the electric fields pass through said region.

5. The apparatus as claimed in any of the preceding Claims, c h a r a c t e r i z e d in that the apparatus includes means (34) for supplying therapeutic substances, genetic material and/or ionizing radiation to said restricted region of a human or of an animal; or that the apparatus is designed to cooperate with such means (34).

6. The apparatus as claimed in any of the preceding Claims, c h a r a c t e r i z e d in that the apparatus includes sensors (8) for detecting electric fields formed by the electrodes (6,15,16,24); and that the sensors are connected to a registration and converter device (10) for calculating the size of the electric field strength in the treatment region; and that, for regulating the amplitude of the voltage pulses applied on the electrodes, the registration and converter device (10) is connected to the high voltage generator (1) and/or to means (2,3,4) connected inbetween the high voltage generator (1) and the electrodes (6,15,16,24).

7. The apparatus as claimed in any of the preceding Claims, c h a r a c t e r i z e d in that the electrodes (6) are disposed to be excited alternatingly and only two at a time.

8. The apparatus as claimed in any of the preceding Claims, c h a r a c t e r i z e d in that the apparatus includes sensors (14) for detecting the distance between the electrodes (6) in each pair of excited electrodes; and that said registration and converter device (10) includes means for adjusting the voltage between the electrodes (6) in each pair of excited electrodes based on the distance between the electrodes.

Fig. 1

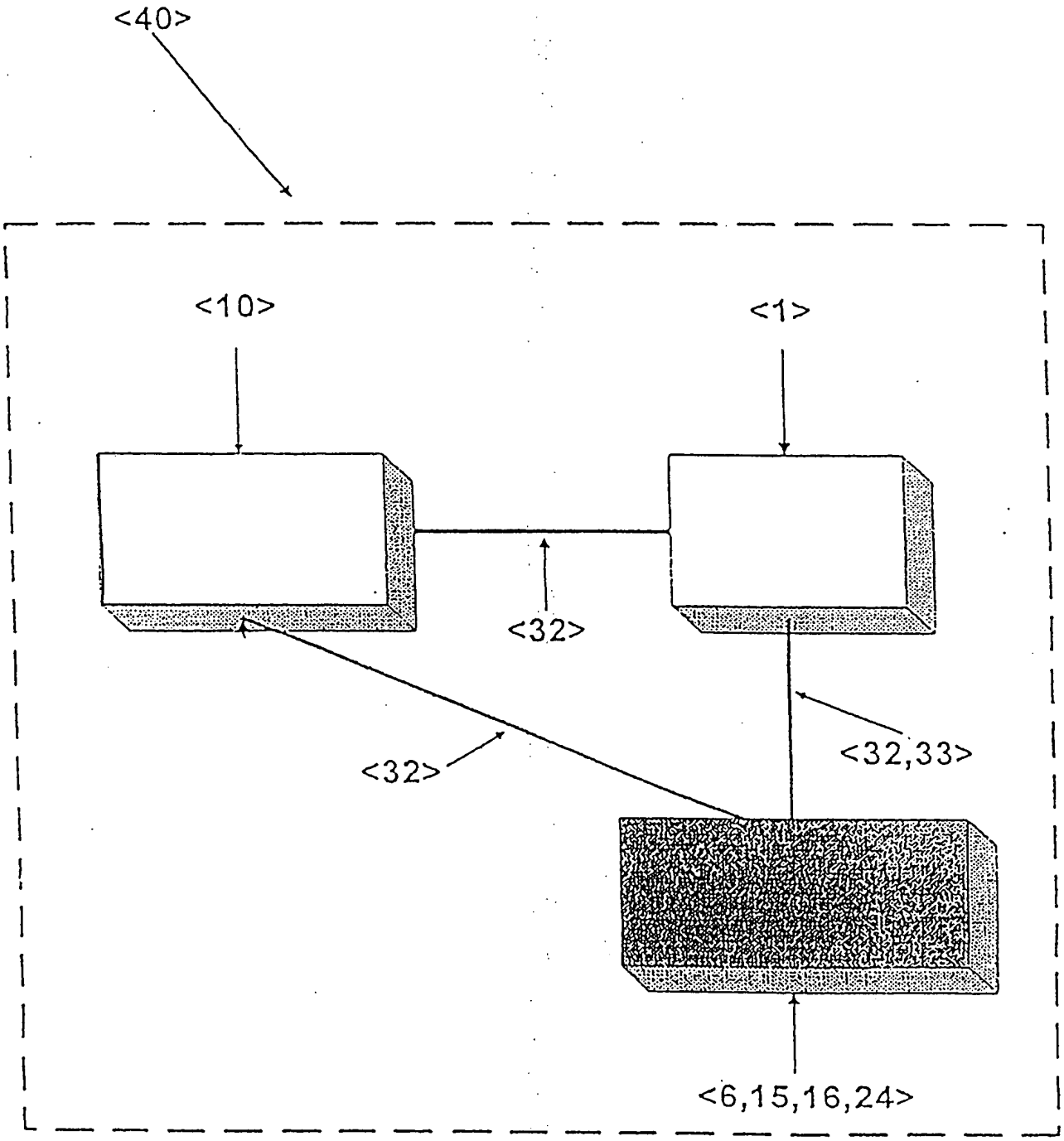


Fig. 2

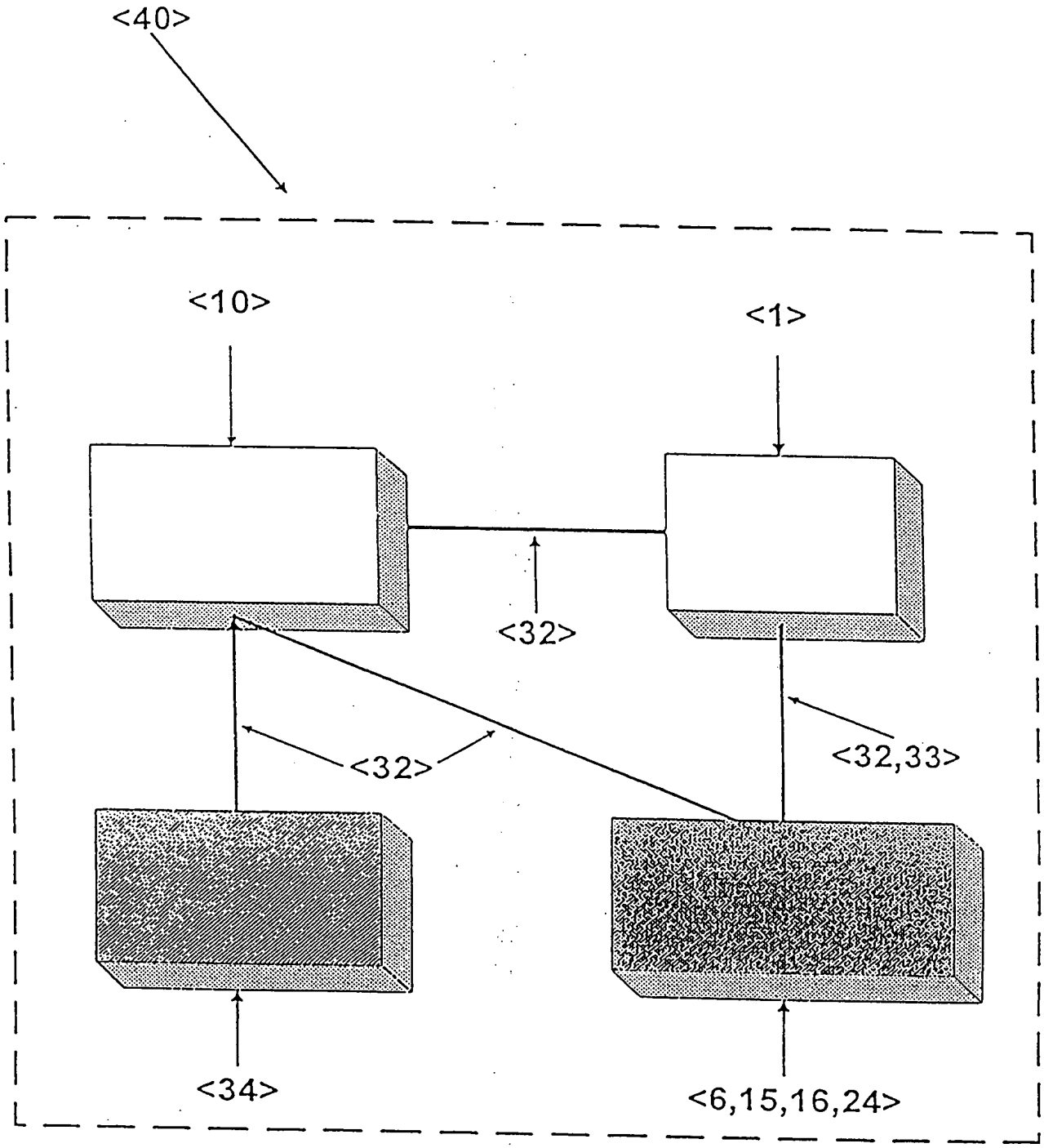


Fig. 3

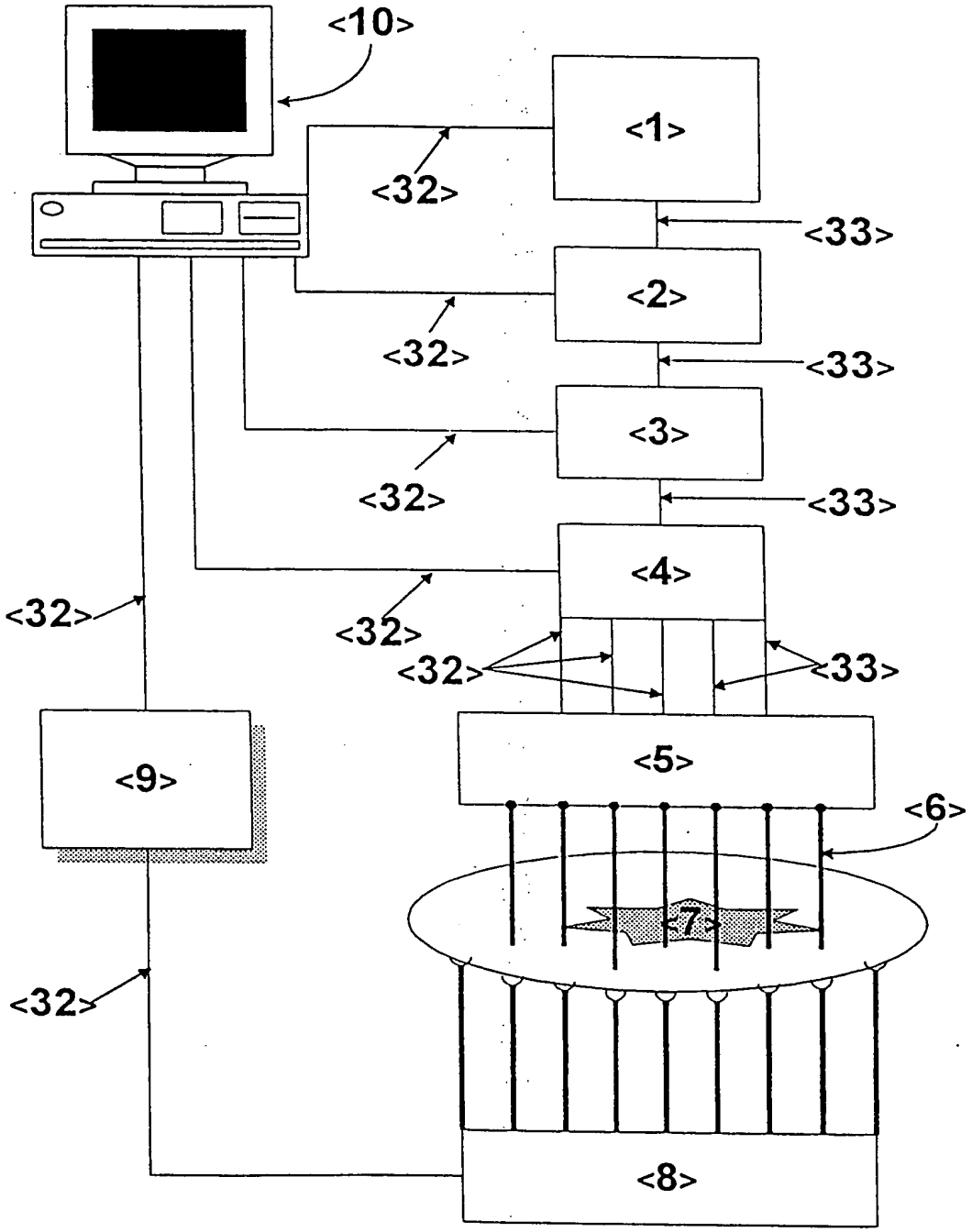
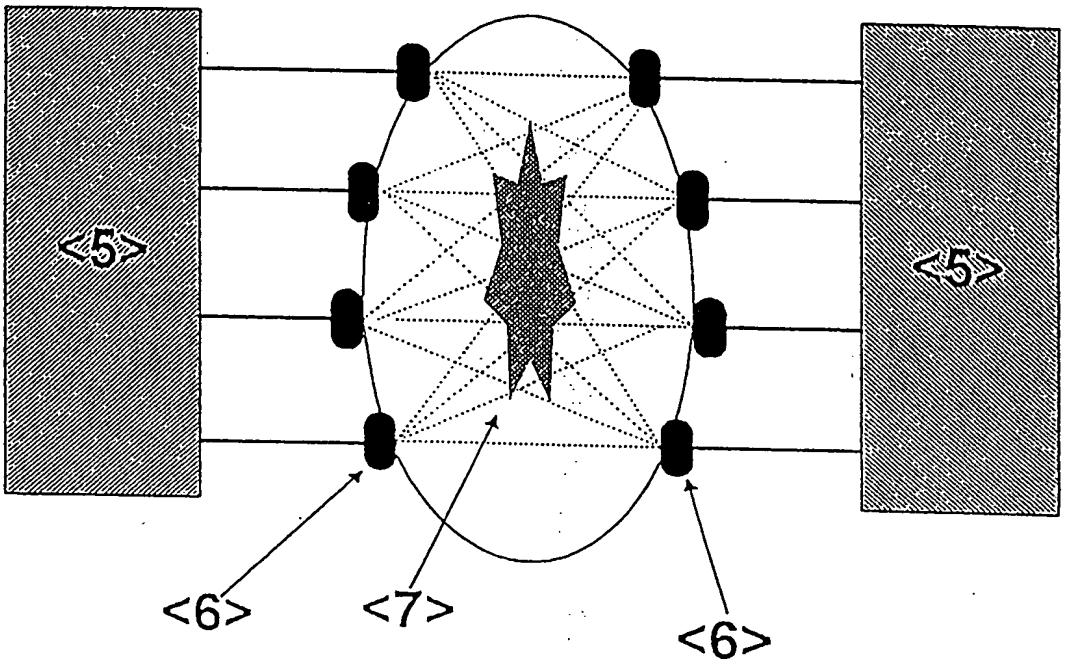


Fig. 4 a,b



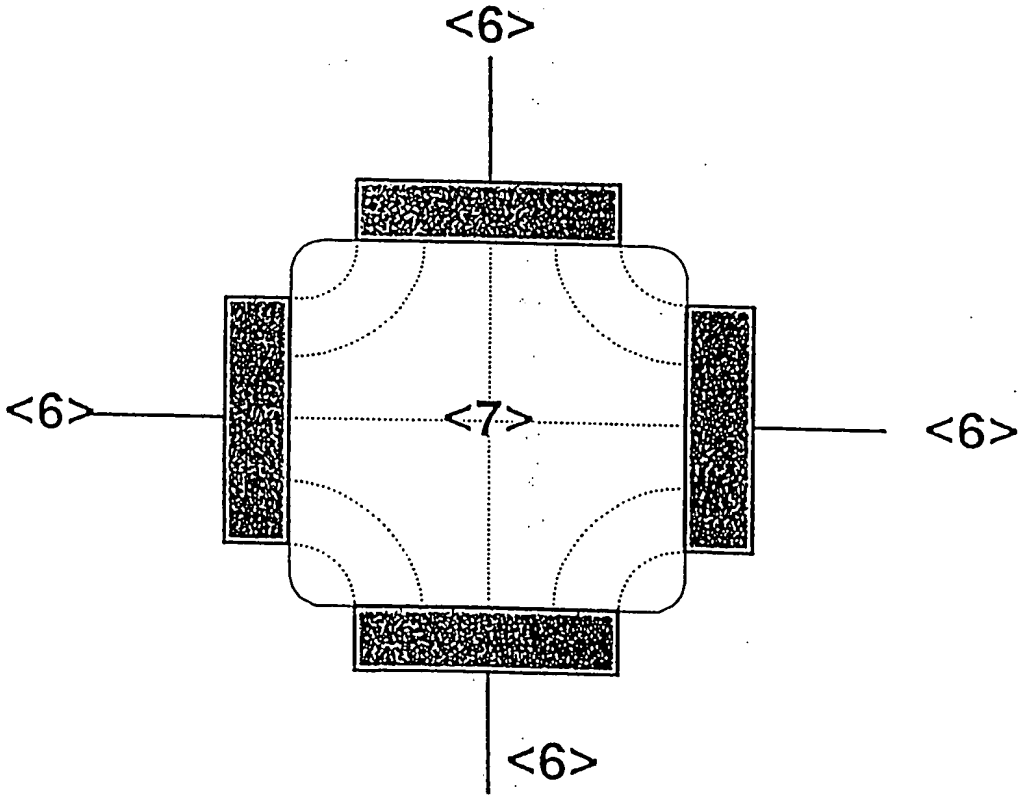


Fig. 4 c,d

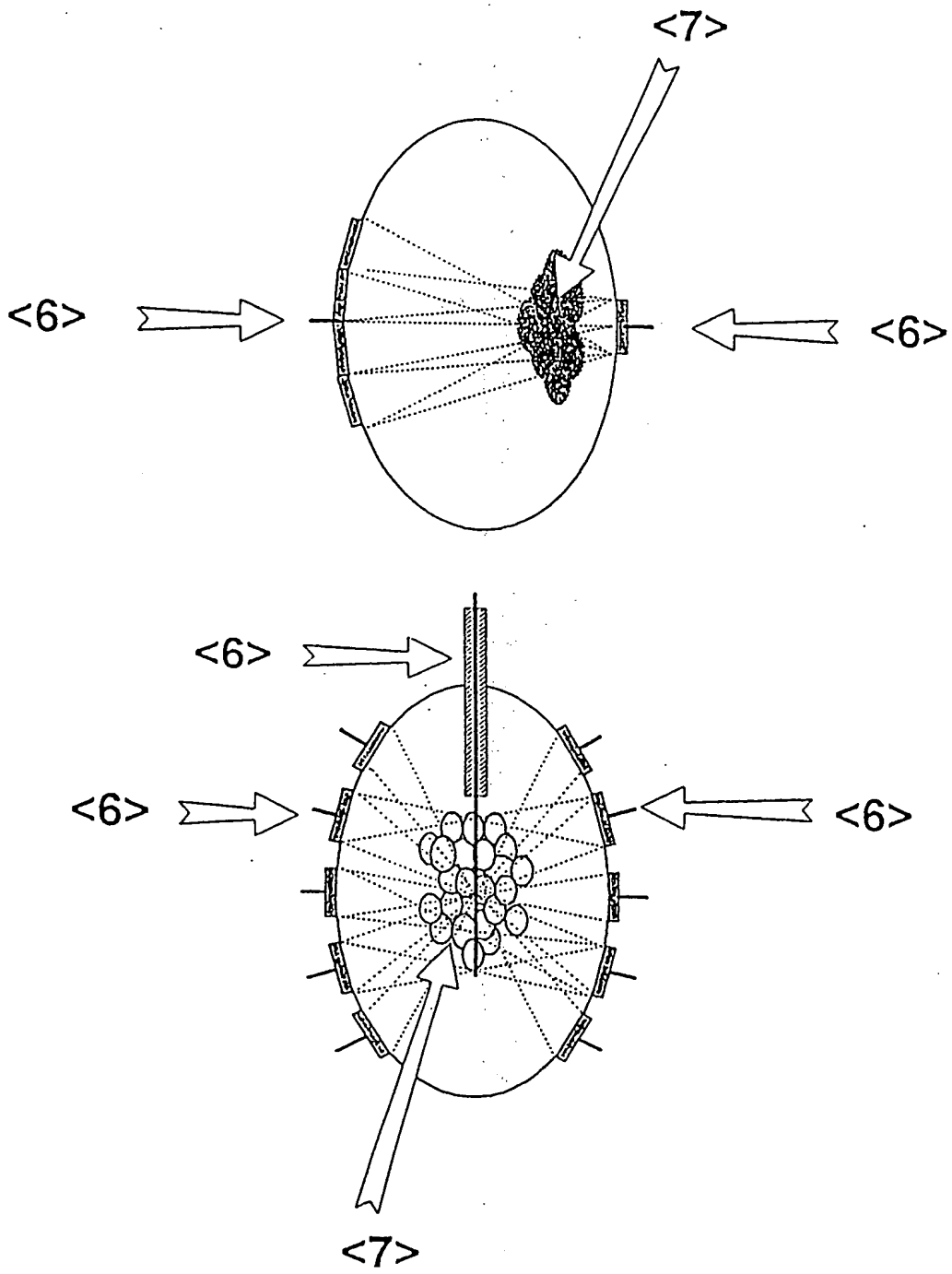
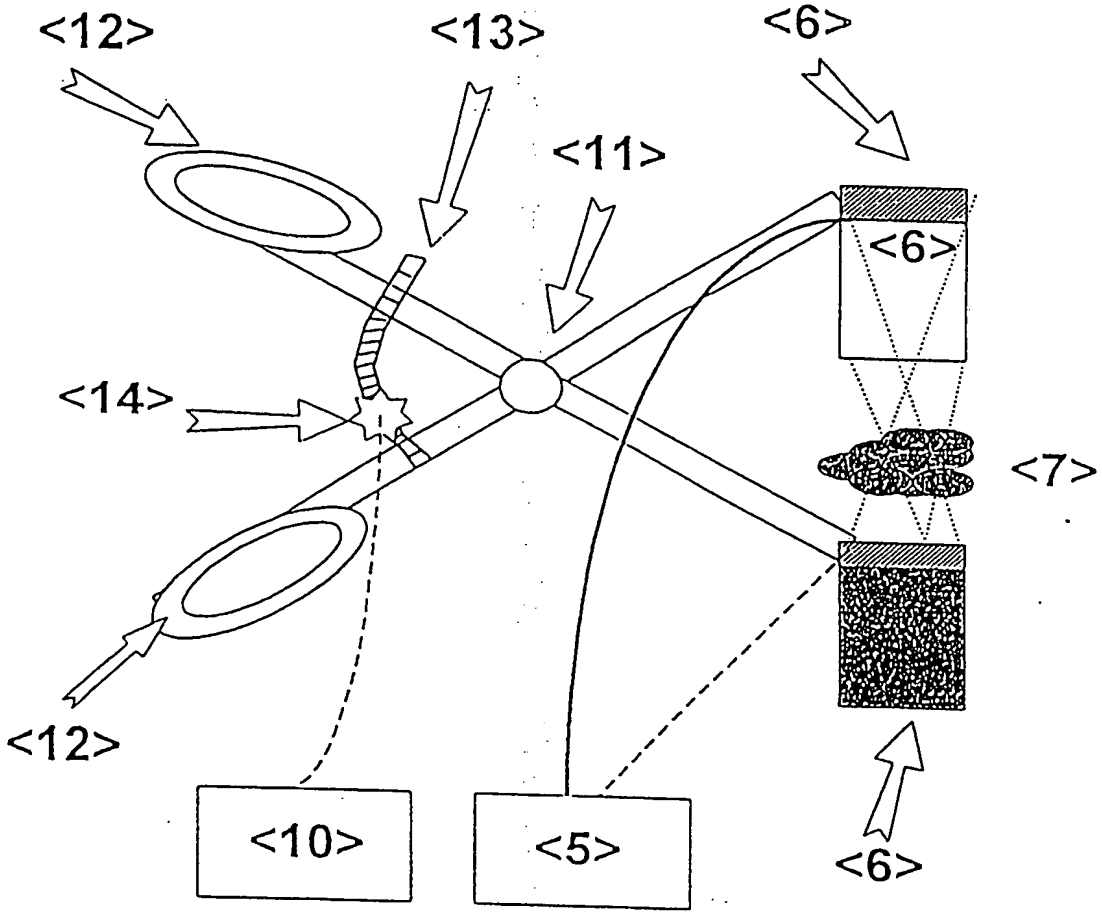


Fig. 5



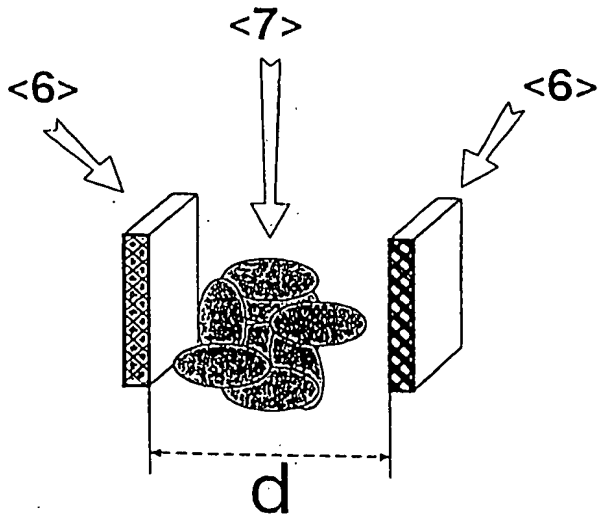


Fig. 6 a

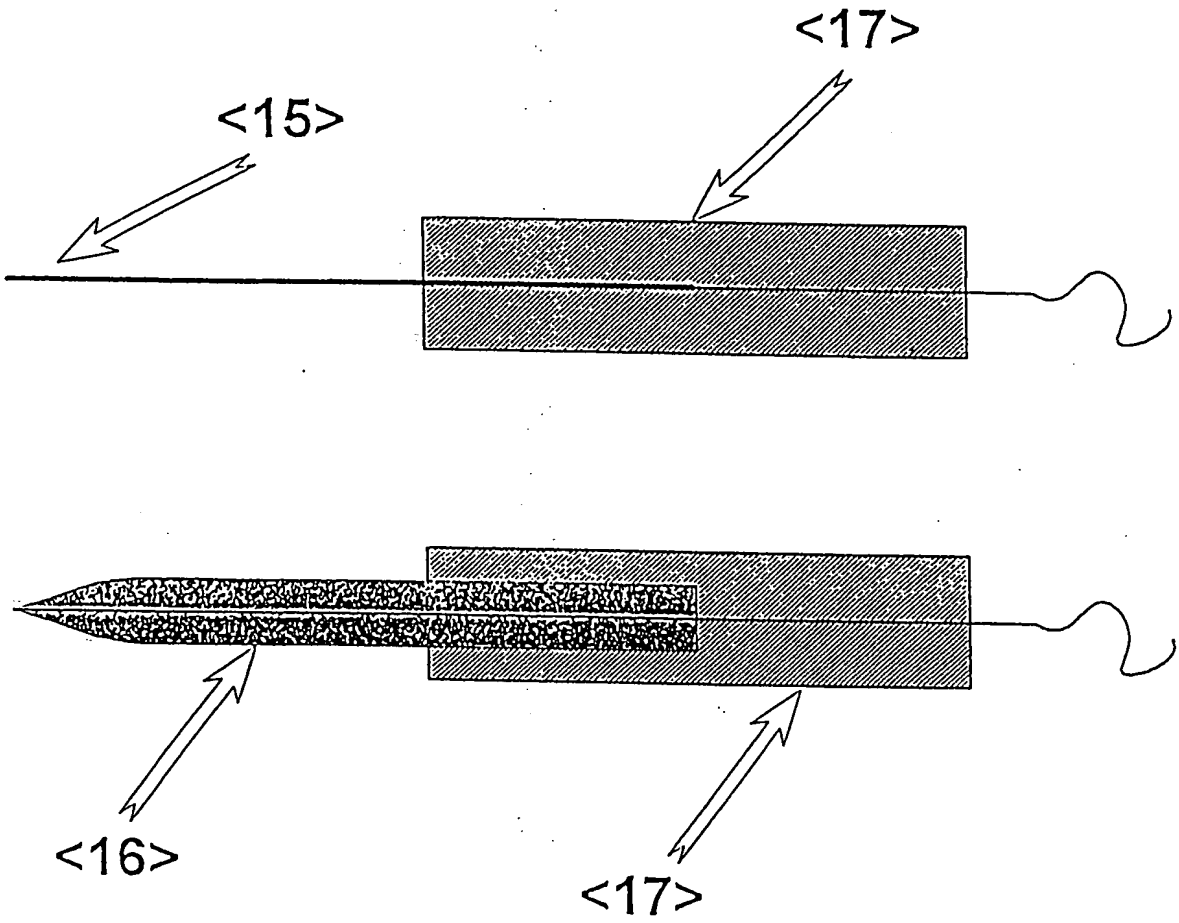


Fig. 6 b

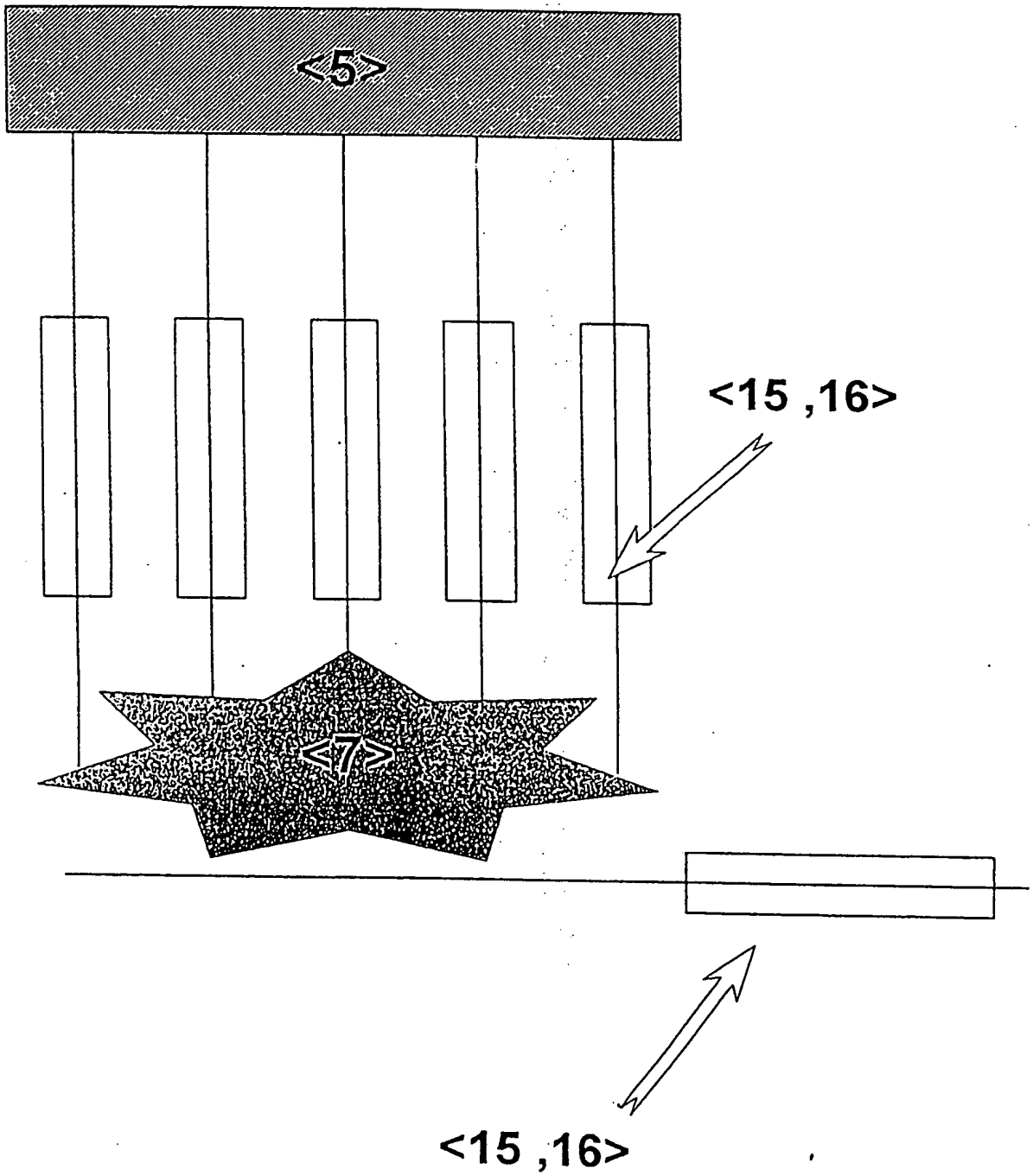


Fig. 6 c

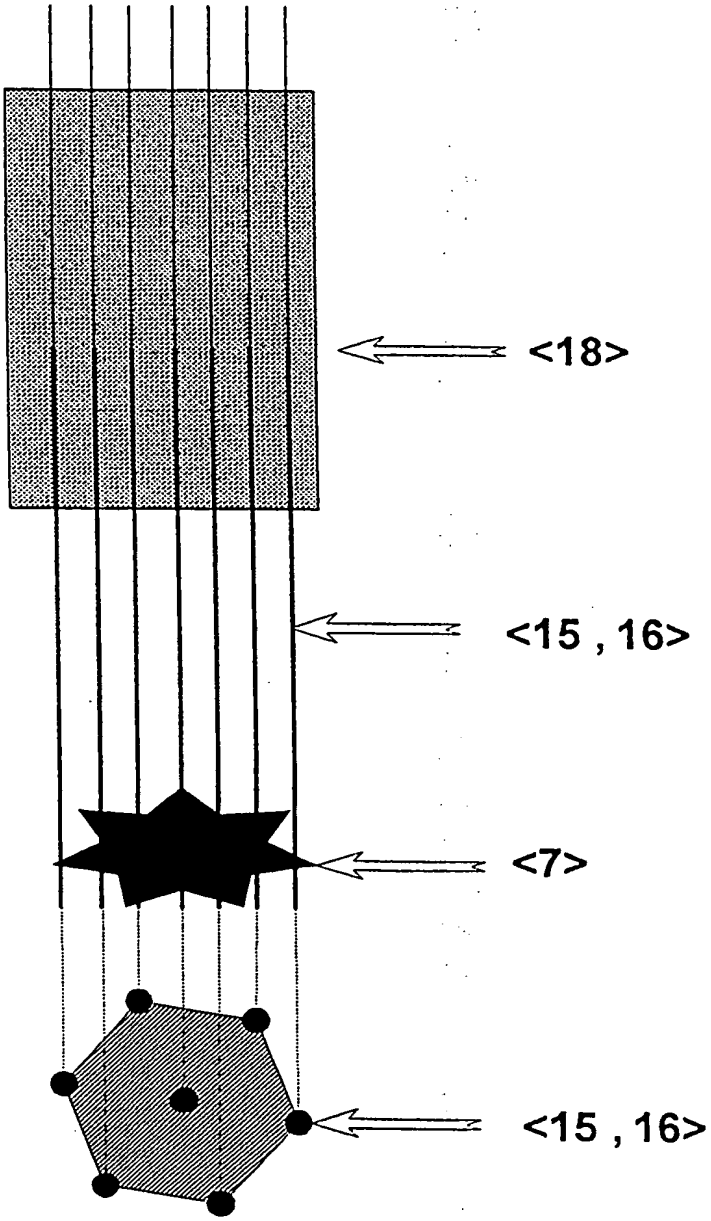


Fig. 6 d

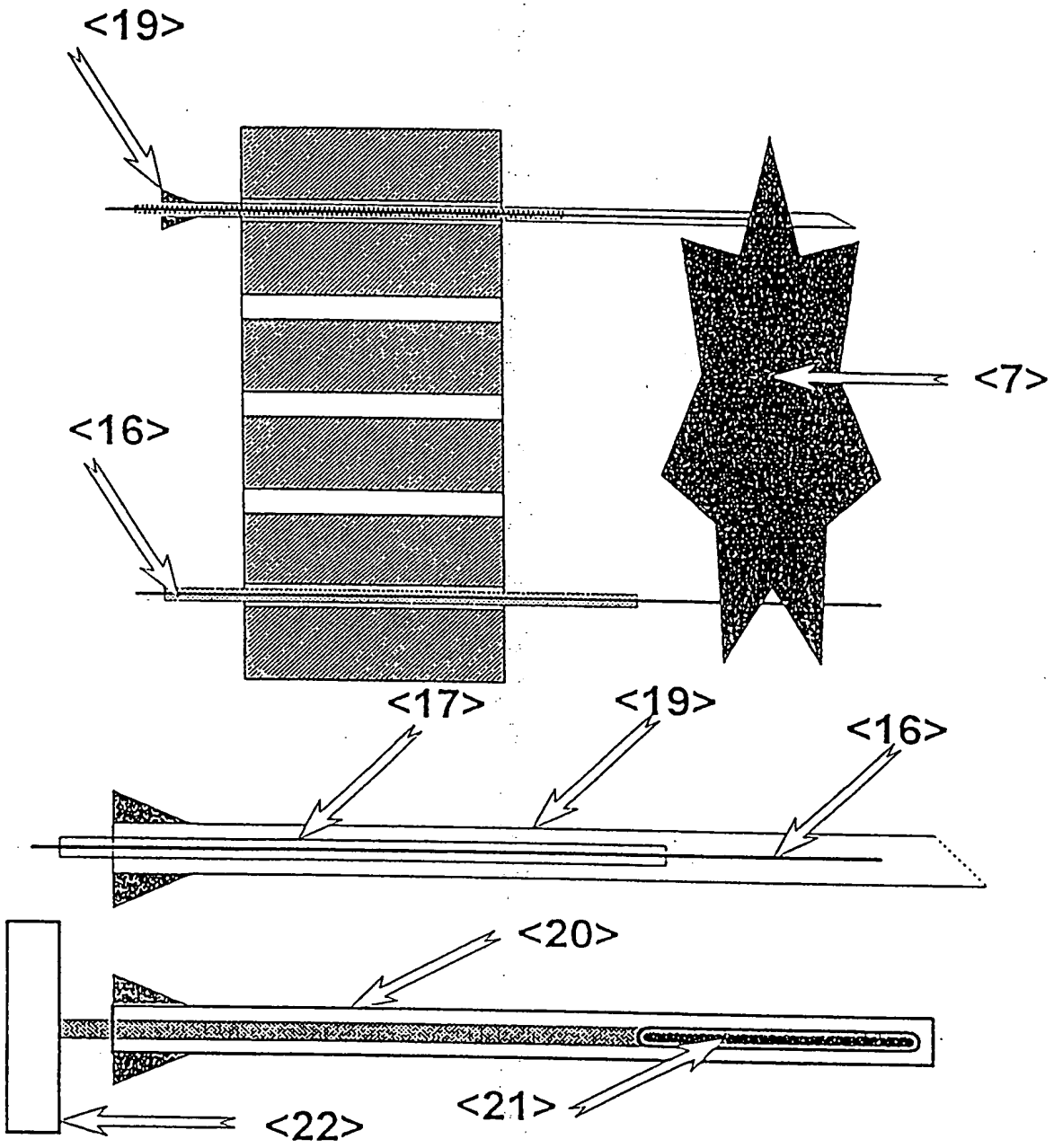


Fig.7 a-c

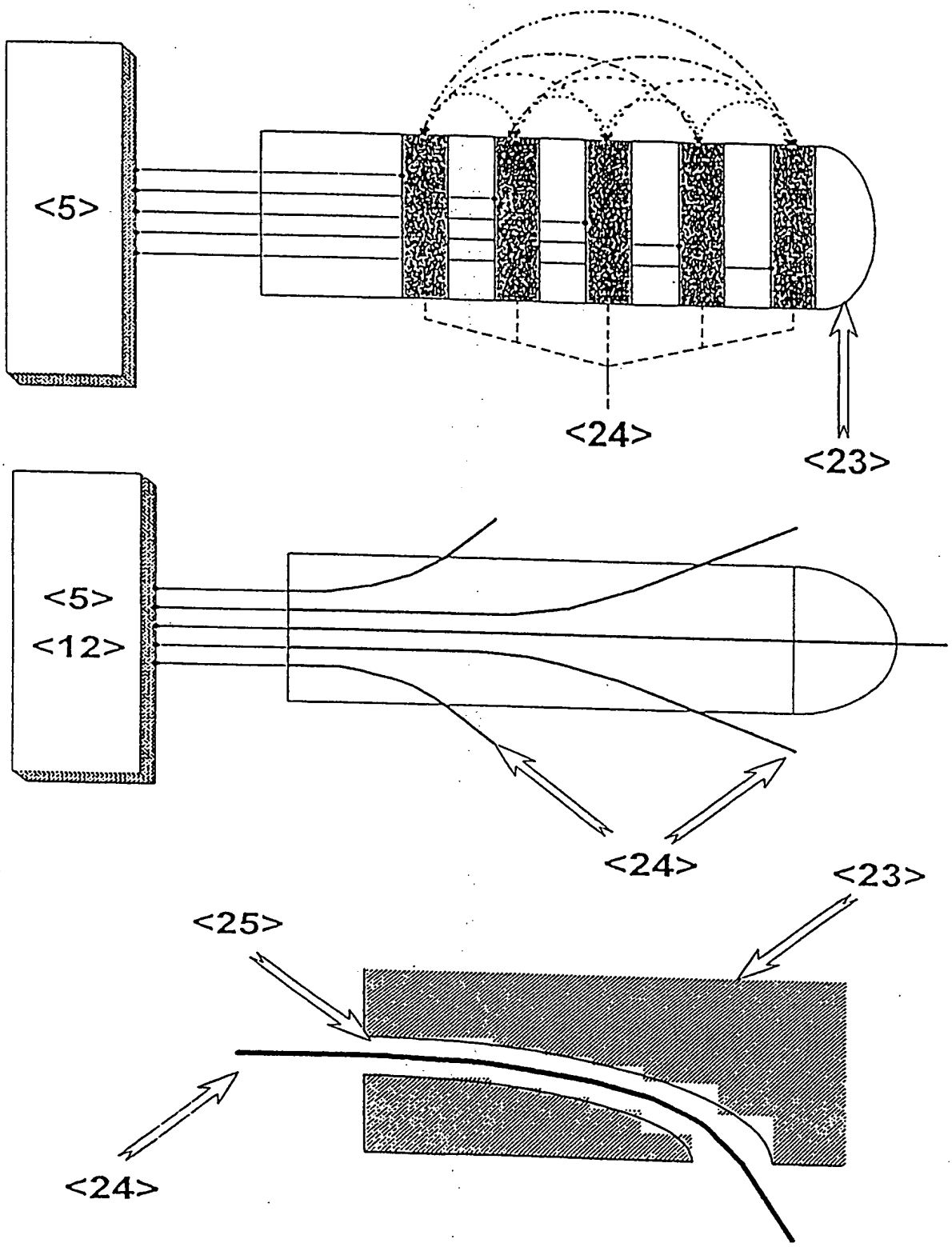


Fig. 8

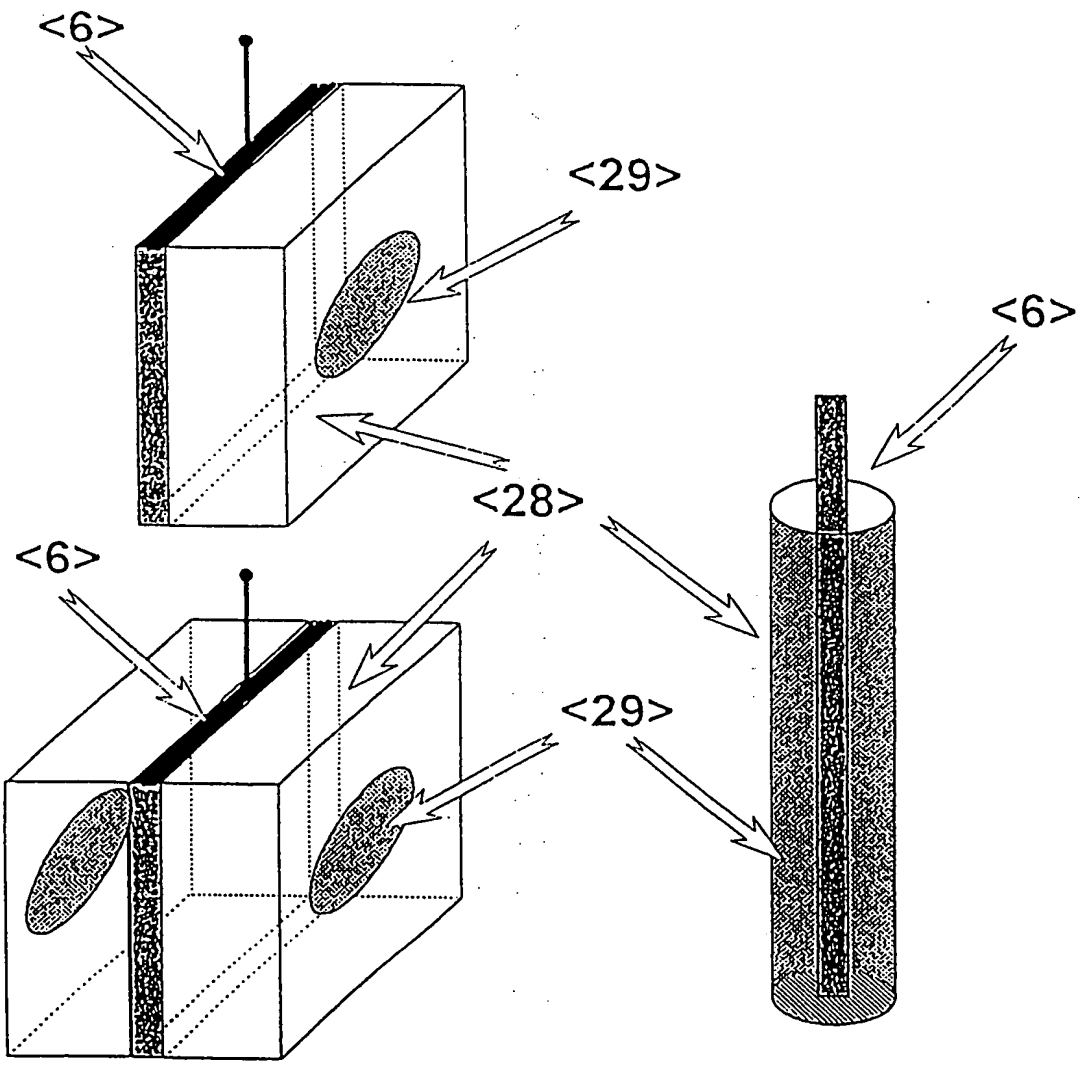


Fig. 9 a-e

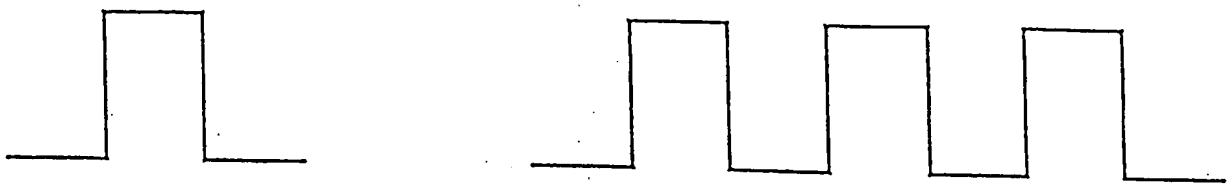


Fig. 9 a

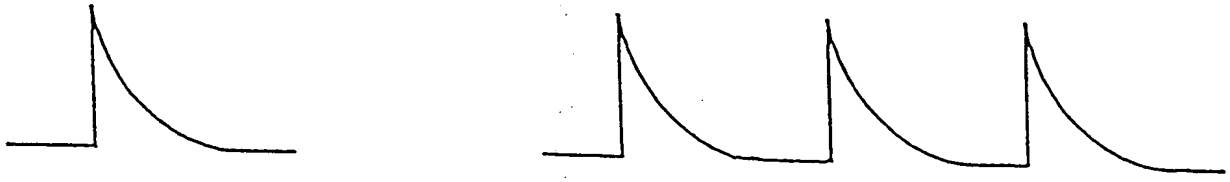


Fig 9 b

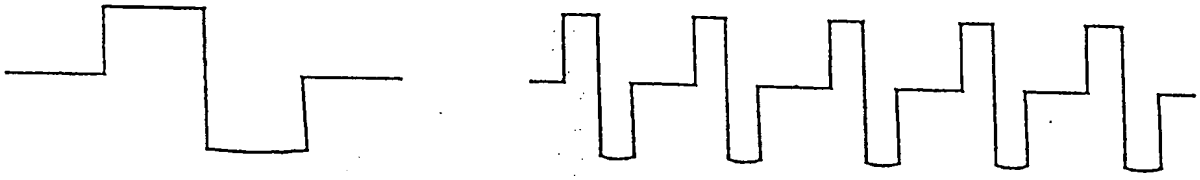


Fig 9 c

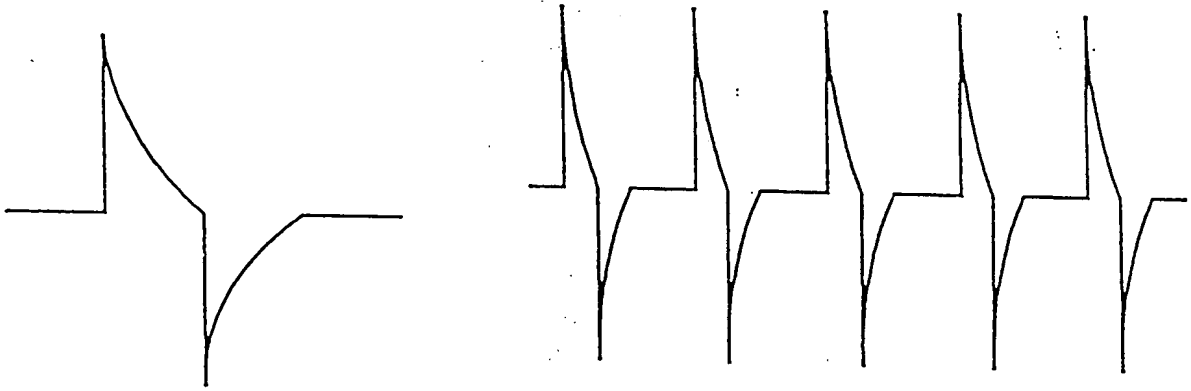


Fig. 9 d

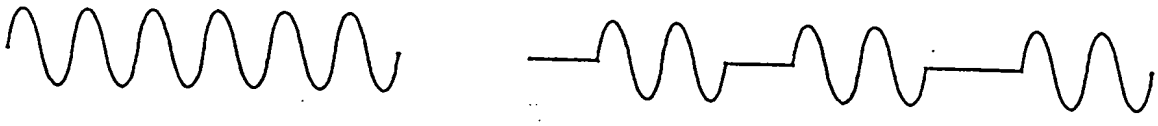


Fig 9 e

Fig. 10

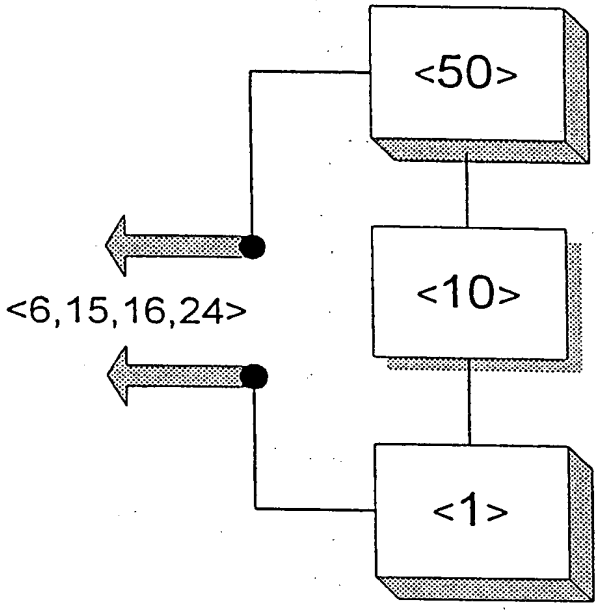
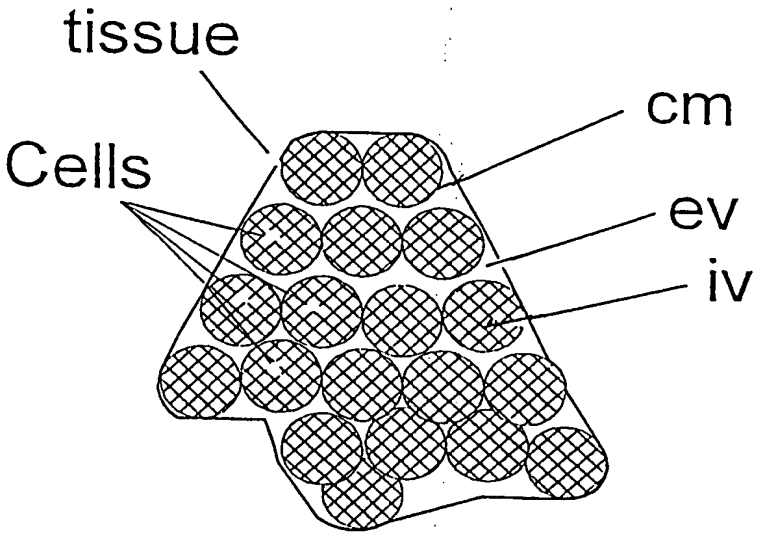


Fig. 11 a,b



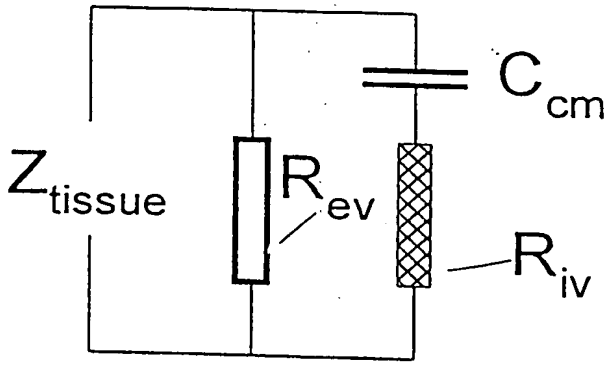
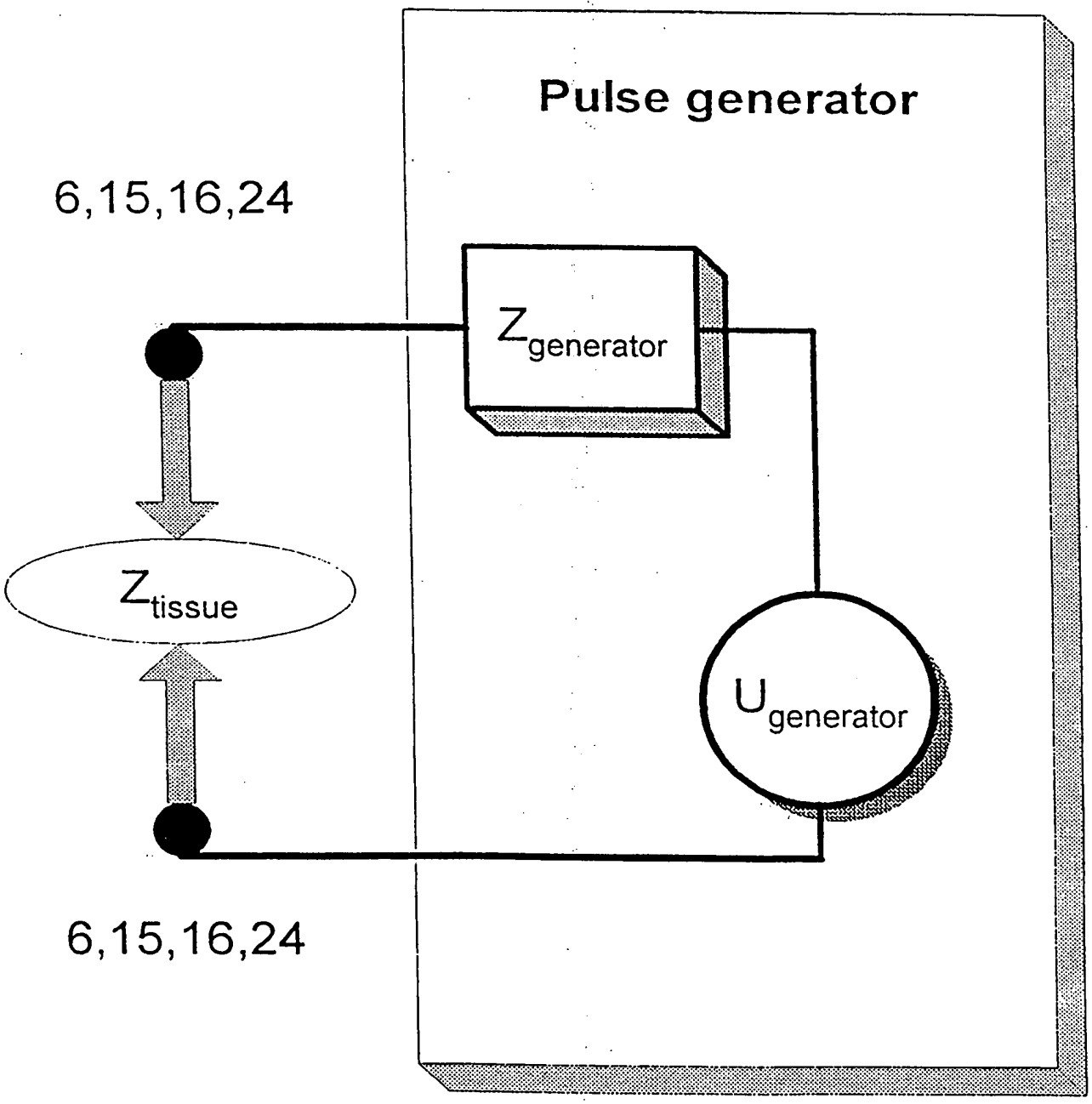


Fig. 12


Pulse generator
6,15,16,24
$Z_{generator}$
Z_{tissue}
$U_{generator}$
6,15,16,24

Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference T/81EI0905/PC	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/DE98/03395	International filing date (*day/month/year*) 17 November 1998 (17.11.98)	Priority date (*day/month/year*) 23 December 1997 (23.12.97)
International Patent Classification (IPC) or national classification and IPC B23Q 11/08		
Applicant EITEC FÜHRUNGSBAHNSCHUTZ-SYSTEME GMBH		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09 July 1999 (09.07.99)	19 January 2000 (19.01.2000)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/DE98/03395

I. Basis of the report

1. This report has been drawn on the basis of (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

☐ the international application as originally filed.

☒ the description, pages 1-15, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____.

☒ the claims, Nos. _____, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. 1-15, filed with the letter of 08 July 1999 (08.07.1999),
Nos. _____, filed with the letter of _____.

☒ the drawings, sheets/fig 1/7-7/7, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____,
sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/DE 98/03395

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step r industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-15	YES
	Claims		NO
Inventive step (IS)	Claims	1-15	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-15	YES
	Claims		NO

2. Citations and explanations

The following documents are referred to:

D1: DE-A-40 33 541 (HENNING GMBH GEB), 23 April 1992
D2: US-A-2 850 332 (BEGLE), 2 September 1958

Document D1, which is considered to be the closest prior art, discloses (cf. Figure 1 and Claim 1) a segmented apron. The subject of Claim 1 of the present application differs from the apron disclosed in D1 in that:

> the portions of the lateral faces which are furthest from the large face of the segment have curved edges which can roll against adjacent segments as the segments pivot relative to each other.

The subject of Claim 1 is therefore novel (PCT Article 33(2)).

The object of the invention can thus be regarded as that of providing a segmented apron with improved bending properties to allow deflection and reeling.

The solution involves an inventive step (PCT Article 33(3)) because it is not disclosed in or suggested by of the documents cited in the international search report.

Document D1 discloses segments of trapezoidal cross-section, which have, instead of curved edges, sloping lateral faces that act as stops and limit the deflection angle (see Claim 6). Figure 5 in D1 shows segments with rounded lateral faces, but these serve merely to prevent overstretching of the segment connectors and do not roll off each other (see D1, column 3, lines 12-31). Furthermore, there is nothing to suggest combining the design features of the embodiment shown in Figure 1 with those shown in Figure 5 in order to arrive at the subject of the present invention. Although the segmented apron according to the embodiment shown in Figure 6 has an apparently closed surface and segments with lateral faces that include a curved portion, there is no rolling motion because in each case an inwardly curving edge and an outwardly curving edge engage each other and guide the faces, the sweeping action being again limited by stops. A similar segmented apron is known from document D2 (see in particular Figure 2).

The claimed solution generates less noise than the prior art solutions referred to. This is because the segments roll off each other and have a greater sweep than the known segmented aprons that form a closed surface when in the extended position.

Claims 2-15 are dependent on Claim 1 and therefore also meet the PCT requirements of novelty and inventive step.

All the claims meet the requirement of industrial applicability (PCT Article 33(4)).

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

1. The description is not consistent with the claims (PCT Rule 5.1(a)(iii)). Specifically, the passage from page 4, line 19 to page 5, line 22 is not consistent with the amendments made to the claims, which causes problems of clarity when the description is used to interpret the claims.

2. Contrary to the requirements of PCT Rule 5.1(a)(ii), the description does not indicate the relevant prior art disclosed in document D1, nor does it cite the said document.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The phrase "...two end portions of circular cross-section extending from one end portion across the central portion to the other end portion" in Claim 14 is unclear and leaves the reader in doubt as to the meaning of the technical feature referred to. The subject of the claim is therefore not clearly defined (PCT Article 6).

For the purposes of the examination it has been assumed that the following formulation applies (cf. page 10, lines 14-20 of the description, and Figures 1-3):

> *"...characterised in that each segment connector (3) has a central portion with parallel upper and lower surfaces, and two end portions of circular cross-section with a diameter greater than the thickness of the central portion."*

PCT REQUEST

PM 445 PC

Original (for **SUBMISSION**) - printed on 29.03.1999 04:09:18 PM

0 0-1	**For receiving Office use only** International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4 0-4-1	**Form - PCT/RO/101 PCT Request** Prepared using	PCT-EASY Version 2.83 (updated 01.03.1999)
0-5	**Petition** The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	**Receiving Office (specified by the applicant)**	Swedish Patent Office (RO/SE)
0-7	**Applicant's or agent's file reference**	PM 445 PC
I	**Title of invention**	AN APPARATUS FOR TREATING DISEASES
II II-1 II-2 II-4 II-5 II-6 II-7	**Applicant** This person is: Applicant for Name Address: State of nationality State of residence	 applicant only all designated States except US ADITUS MEDICAL AB Bålabäcksvägen 1 S-SE-240 36 Stehag Sweden SE SE
III-1 III-1-1 III-1-2 III-1-4 III-1-5 III-1-6 III-1-7	**Applicant and/or inventor** This person is: Applicant for Name (LAST, First) Address: State of nationality State of residence	 applicant and inventor US only PERSSON, Bertil Angantyrsgränd 19 S-SE-224 75 Lund Sweden SE SE

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PCT REQUEST PM 445 PC

Original (for **SUBMISSION**) - printed on 29.03.1999 04:09:18 PM

III-2	**Applicant and/or inventor**	
III-2-1	This person is:	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	BÖHMER, Bernt
III-2-5	Address:	Bålabäcksvägen 1 S-SE-240 36 Stehag Sweden
III-2-6	State of nationality	SE
III-2-7	State of residence	SE
III-3	**Applicant and/or inventor**	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	THORVINGER, Bo
III-3-5	Address:	Humlebäcksgatan 43 S-SE-216 20 Malmö Sweden
III-3-6	State of nationality	SE
III-3-7	State of residence	SE
IV-1	**Agent or common representative; or address for correspondence** The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name	MAGNUPATENT AB
IV-1-2	Address:	Mr. Gustav Magnusson Mr. Leif Karlsson P.O. Box 6207 S-200 11 MALMÖ Sweden
IV-1-3	Telephone No.	040-701 55
IV-1-4	Facsimile No.	040-12 26 11
IV-1-5	e-mail	magnupatent@magnupatent.se

PCT REQUEST PM 445 PC

Original (for **SUBMISSION**) - printed on 29.03.1999 04:09:18 PM

V	**Designation of States**	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW SD SZ UG ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
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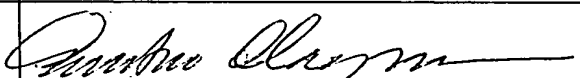
V-5	**Precautionary Designation Statement** In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-6	**Exclusion(s) from precautionary designations**	NONE
VI-1	**Priority claim of earlier national application**	
VI-1-1	Filing date	31 March 1998 (31.03.1998)
VI-1-2	Number	9801139-8
VI-1-3	Country	SE
VI-2	**Priority document request** The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1

PCT REQUEST PM 445 PC

Original (for SUBMISSION) - printed on 29.03.1999 04:09:18 PM

VII-1	International Searching Authority Chosen	Swedish Patent Office (ISA/SE)	
VII-2	Request to use results of earlier search; reference to that search		
VII-2-1	Date	31 March 1998 (31.03.1998)	
VII-2-2	Number	SE 98/00421	
VII-2-3	Country (or regional Office)	SE	
VIII	Check list	number of sheets	electronic file(s) attached
VIII-1	Request	4	-
VIII-2	Description	18	-
VIII-3	Claims	4	-
VIII-4	Abstract	1	sammanfattning.txt
VIII-5	Drawings	16	-
VIII-7	TOTAL	43	
	Accompanying items	paper document(s) attached	electronic file(s) attached
VIII-8	Fee calculation sheet	✓	-
VIII-16	PCT-EASY diskette	-	diskette
VIII-18	Figure of the drawings which should accompany the abstract	10	
VIII-19	Language of filing of the international application	Swedish	
IX-1	Signature of applicant or agent		
IX-1-1	Name	MAGNUPATENT AB	
IX-1-2	Name of signatory	Gustav Magnusson	

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10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/SE
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	

PCT (ANNEX - FEE CALCULATION SHEET)

PM 445 PC

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(This sheet is not part of and does not count as a sheet of the international application)

0 0-1	**For receiving Office use only** International Application No.	
0-2	Date stamp of the receiving Office	

0-4 0-4-1	**Form - PCT/RO/101 (Annex)** **PCT Fee Calculation Sheet** Prepared using		PCT-EASY Version 2.83 (updated 01.03.1999)		
0-9	**Applicant's or agent's file reference**		PM 445 PC		
2	**Applicant**		ADITUS MEDICAL AB, et al.		
12	**Calculation of prescribed fees**		fee amount/multiplier	total amounts (SEK)	
12-1	Transmittal fee	T	⇨	1 000	
12-2	Search fee	S	⇨	6 200	
12-3	International fee Basic fee (first 30 sheets)	b1	3 500		
12-4	Remaining sheets		13		
12-5	Additional amount	(X)	80		
12-6	Total additional amount	b2	1 040		
12-7	b1 + b2 =	B	4 540		
12-8	Designation fees Number of designations contained in international application		79		
12-9	Number of designation fees payable (maximum 10)		10		
12-10	Amount of designation fee	(X)	800		
12-11	Total designation fees	D	8 000		
12-12	PCT-EASY fee reduction	R	-1 080		
12-13	Total International fee (B+D-R)	I	⇨	11 460	
12-14	Fee for priority document Number of priority documents requested		1		
12-15	Fee per document	(X)	0		
12-16	Total priority document fee	P	⇨	0	
12-17	**TOTAL FEES PAYABLE (T+S+I+P)**		⇨	18 660	
12-19	**Mode of payment**		other: within one month		

VALIDATION LOG AND REMARKS

13-2-1	**Validation messages** **Request**	Green? A translation of the international application into English will have to be prepared under the responsibility of the ISA selected.

PCT (ANNEX - FEE CALCULATION SHEET) PM 445 PC

Original (for SUBMISSION) - printed on 29.03.1999 04:09:18 PM

		Green? Please note that the entire request (including the title of invention) must be in English
13-2-3	Validation messages Names	Yellow Applicant 1.:Street address missing
		Green? Applicant 1.:Telephone No. missing
		Green? Applicant 1.:Facsimile No. missing
		Yellow Applicant 2.:Street address missing
		Yellow Applicant 3.:Street address missing
		Yellow Applicant 4.:Street address missing
13-2-6	Validation messages Contents	Yellow! The power of attorney or a copy of the general power of attorney will need to be furnished unless all applicants sign the request form.
13-2-7	Validation messages Fees	Green? Please verify that modified fee amounts are correct.

RECORD COPY

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PCT REQUEST

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0 0-1	For receiving Office use only International Application No.	PCT/SE99/00511
0-2	International Filing Date	30 -03- 1999
0-3	Name of receiving Office and "PCT International Application"	The Swedish Patent Office PCT International Application
0-4 0-4-1	Form - PCT/RO/101 PCT Request Prepared using	PCT-EASY Version 2.83 (updated 01.03.1999)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
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II II-1 II-2 II-4 II-5 II-6 II-7	Applicant This person is: Applicant for Name Address: State of nationality State of residence	 applicant only all designated States except US ADITUS MEDICAL AB Bålabäcksvägen 1 S-SE-240 36 Stehag Sweden SE SE
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III-3-5	Address:	Humlebäcksgatan 43 S-SE-216 20 Malmö Sweden
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IV-1-2	Address:	Mr. Gustav Magnusson Mr. Leif Karlsson P.O. Box 6207 S-200 11 MALMÖ Sweden
IV-1-3	Telephone No.	040-701 55
IV-1-4	Facsimile No.	040-12 26 11
IV-1-5	e-mail	magnupatent@magnupatent.se

PCT REQUEST

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V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW SD SZ UG ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
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V-6	**Exclusion(s) from precautionary designations**	NONE
VI-1	**Priority claim of earlier national application**	
VI-1-1	Filing date	31 March 1998 (31.03.1998)
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PCT REQUEST

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VII-1	**International Searching Authority Chosen**	Swedish Patent Office (ISA/SE)	
VII-2	**Request to use results of earlier search; reference to that search**		
VII-2-1	Date	31 March 1998 (31.03.1998)	
VII-2-2	Number	SE 98/00421	
VII-2-3	Country (or regional Office)	SE	
VIII	**Check list**	number of sheets	electronic file(s) attached
VIII-1	Request	4 ✓	-
VIII-2	Description	18 ✓	-
VIII-3	Claims	4 ✓	-
VIII-4	Abstract	1 ✓	sammanfattning.txt
VIII-5	Drawings	16 ✓	-
VIII-7	TOTAL	43 ✓	
	Accompanying items	paper document(s) attached	electronic file(s) attached
VIII-8	Fee calculation sheet	✓	-
VIII-16	PCT-EASY diskette	-	diskette
VIII-18	**Figure of the drawings which should accompany the abstract**	10	
VIII-19	**Language of filing of the international application**	Swedish	
IX-1	**Signature of applicant or agent**		
IX-1-1	Name	MAGNUPATENT AB	
IX-1-2	Name of signatory	Gustav Magnusson	

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10-2	**Drawings:**	
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10-2-2	Not received	
10-3	**Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application**	
10-4	**Date of timely receipt of the required corrections under PCT Article 11(2)**	
10-5	**International Searching Authority**	ISA/SE
10-6	**Transmittal of search copy delayed until search fee is paid**	

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11-1	**Date of receipt of the record copy by the International Bureau**	18 MAY 1999 (18.05.99)

Anordning för behandling av sjukdomar

Föreliggande uppfinning avser en anordning för generering av pulser av elektriska fält i ett begränsat område hos en människa eller ett djur enligt ingressen till det oberoende patentkravet.

De terapiformer som rutinmässigt används inom modern sjukvård för tumörterapi är exempel på behandlingar där utfallet av behandlingarna är otillfredsställande. Vid t ex tumörterapi misslyckas man ofta med att åstadkomma lokal tumörkontroll vilket är dödsorsaken hos ca 30% av cancerpatienter. Det är därför viktigt att utveckla ny och förbättrad teknik för lokal och regional tumörbehandling.

I dagens sjukvård är kirurgi, kemterapi och strålterapi även benämnd strålbehandling eller kombinationer härav de vanligast använda metoderna för behandling av maligna tumörer. Ungefär varannan patient med infiltrerande cancer behandlas med strålterapi men endast ca hälften av patienterna blir botade. Misslyckandet beror dels på förekomsten av spridd sjukdom (fjärrmetastaser) eller recidiv (återväxt av tumör i behandlingsområdet), dels på att vissa tumörformer är resistenta mot strålbehandling eller kemterapi.

Med varierande framgång har man försökt att förstärka och förbättra strålterapins effektivitet att sterilisera tumörer. Man har t ex använt sig av mer sofistikerade strålterapitekniker, såsom stereotaktisk behandling, "conformal radiotherapy", av ändrad fraktionering eller tillfört läkemedel för att öka strålkänsligheten hos tumörerna.

Man använder också värme som adjuvant till joniserande strålning vilket för vissa tumörformer kan öka antalet kompletta remissioner med upp till en faktor två.

Även vid vissa rent medicinskt behandlade sjukdomar i lokala organ är ibland utfallet av behandlingarna otillräckligt. Det är uppenbart att utöver de önskemål som föreligger beträffande bättre teknik för behandling av t ex tumörer föreligger det såväl önskemål som behov av en mer effektiv teknik för behandling av vissa andra sjukdomar. Vid t ex lokal behandling av lokala organ eller tumörer är det till stor fördel om man vid varje behandlingstillfälle har möjlighet att anpassa behandlingens intensitet efter den status vävnaden har i det lokala område eller i det organ som behandlas.

Enligt uppfinningen använder man sig av en serie korta högspänningspulser för att alstra ett elektriskt fält i det lokala område eller i det organ som skall behandlas. I den fortsatta beskrivningen används även uttrycket Högvolts Impuls Terapi ibland förkortat till HVIT.

Behandlingen med elektriska fält åstadkommer en perforering av cellmembranen vilka därigenom tillåter passage av till kroppen tillförda ämnen (t ex cytostatika eller genetiskt material). Behandlingen medför ökat inflöde av terapeutiska substanser varigenom effekterna hos kemterapi förstärks. Utflöde av specifika ämnen ur t ex perforerade tumörceller åstadkommer därtill ofta en stimulering av immunsystemet. Vid total dielektrisk kollaps uppnås ofta att cellerna steriliseras direkt av det av högspänningspulsen bildade elektriska fältet. Metoden har vid kliniska försök visat sig vara effektiv i kombination med cytostatika (Bleomycin) för t ex behandling av melanom och tumörer i hals, huvud, lever, pankreas och lungor.

Vid HVIT bestäms behandlingsresultatet av hur många och hur långa högspänningspulser man utsätter vävnaden för och av hur hög elektrisk fältstyrka de pålagda pulserna skapar i vävnaden samt av den form eller frekvens pulserna har. För att få en effektiv och säker behandling måste alla dessa fysikaliska parametrar kunna kontrolleras. Biologiska egenskaper som påverkar behandlingsresultatet är bl a vävnadens elektriska ledningsförmåga, dielektriska egenskaper, cellstorleken och cellmembranens struktur. Alla dessa egenskaper varierar mellan olika vävnader. För att uppnå optimal behandlingseffekt är det därför nödvändigt att mäta hur vävnadens elektriska egenskaper förändras mellan varje högspänningspuls eller mellan serierna av pulser dvs fastställa när cellerna är tillräckligt perforerade.

Vid tidigare använd HVIT var det inte möjligt att kontrollera när vävnaden var tillräckligt perforerad dvs färdigbehandlad, vilket medförde att man ibland underbehandlade och ibland överbehandlade vävnaden. Detta medförde en osäkerhet i behandlingsresultatet. En typisk HVIT behandling enligt tidigare tillämpad teknik innebar att man placerade en applikator över den vävnad som man avsåg att behandla. Högspänningspulsgeneratorn ställdes t ex in så att utspänningen motsvarade en fältstyrka i målvolymen på ca 1300 V/cm. Behandlingen genomfördes med ett fixt antal pulser som man visste vanligen gav önskat resultat. Svagheterna i detta förfarande var dels att man inte visste storleken på det elektriska fält som generatorn i realiteten genererade i målvolymens vävnad, dels att man inte hade någon möjlighet att bedöma när behandlingen var tillräcklig.

Uppfinningen avser en anordning vari ingår mekaniska organ för att utsätta en vävnad inom ett begränsat område eller ett organ hos en människa eller hos ett djur för en eller flera pulser av ett elektriskt fält med en för det aktuella behandlingstillfället inställbar fältstyrka, form, varaktighet och frekvens. Med uttrycket "varaktighet" avses såväl pulsernas längd som antalet pulser, med uttrycket "frekvens" avses såväl hur ofta pulserna upprepas som den frekvens med vilken fältet växlar under pågående puls.

Den kännetecknande delen av det oberoende patentkravet anvisar en teknik som medför en väsentlig förbättring av kirurgins, kemterapins och strålterapins effektivitet. Tekniken är även tillämpbar inom modern molekylärmedicin där man skräddarsyr substanser och genetiska DNA-sekvenser som skall föras in i vävnadsceller.

I de beroende patentkraven anges ytterligare ändamålsenliga utföringsformer av uppfinningen.

Uppfinningen beskrivs närmare med hänvisning till ett antal figurer, vilka visar i:

fig 1 ett blockschema för en principiell anordning för applicering av elektriska fält i ett begränsat område hos en människa eller ett djur.

fig 2 ett blockschema för en principiell anordning för applicering av elektriska fält och/eller joniserande strålning i ett begränsat område hos en människa eller ett djur.

fig 3 ett blockschema för en utföringsform av en kombination av organ för bildandet av elektriska fält i ett begränsat område hos en människa eller ett djur.

fig 4a-d utföringsformer av elektrodapplikatorer för extern behandling av vävnad.

fig 5 en utföringsform av en elektrodapplikator för intraoperativ behandling av t ex tumörer och ytliga tumörnoduler.

fig 6a-d utföringsformer av elektroder och elektrodapplikatorer utformade för interstitiell behandling av vävnad.

fig 7a-c utföringsformer av elektroder och elektrodapplikatorer utformade för behandling av t ex tumörer i kroppskaviteter och i organ åtkomliga via stora kärl.

fig 8 utföringsformer av elektroderna i vilka dessa är anordnade för kombinationsbehandling med antitumorala läkemedel.

fig 9a-e exempel på former hos spänningspulser som påläggs elektroderna.

fig 10 ett förenklat blockschema för en utföringsform av anordningen.

fig 11a en modell för den principiella strukturen hos levande vävnad.

fig 11b ett elektriskt principschema för den elektriska strukturen hos levande vävnad och

fig 12 en elektrisk modell för en pulsgenerator ansluten till levande vävnad.

I fig 1 visas i ett blockschema den principiella utformningen av en högspänningsgenerator 1, elektroder 6,15,16,24 och ett registrerings- och omräkningsorgan 10 t ex en dator eller en mikroprocessor 10 vilka organ samtliga ingår i anordningen enligt uppfinningen. I fortsättningen används för registrerings- och omräkningsorganet utan någon begränsande innebörd även ordet dator. Mellan högspänningsgeneratorn 1 och elektroderna 6,15,16,24 är anordnat en eller flera signalförbindelser 32 och elektriska ledare 33. Mellan datorn 10 och högspänningsgeneratorn 1 och mellan datorn och elektroderna 6,15,16,24 är anordnat en eller flera signalförbindelser 32. Även om signalförbindelserna 32 i figuren är visade som direkt förbindande datorn och elektroderna, är det uppenbart att anordningen som sådan även innefattar i den fortsatta beskrivningen beskrivna organ, såsom brytare 3, fördelardosa 4, elektrodapplikator 5 etc för styrning av spänningssättningen av elektroderna etc.

I figur 2 visas en utföringsform av uppfinningen där en strålningssändare 34 via signalförbindelser 32 är ansluten till datorn. I vissa utföringsformer är strålningssändaren mekaniskt sammanbygd med högspänningsgeneratorn medan den i andra utföringsformer endast har signalförbindelser med den i figur 1 visade kombinationen av organ.

I figur 3 visas schematiskt en utföringsform av en kombination av organ för att i en anordning enligt uppfinningen bilda elektriska fält. I figuren visas block för en högspänningsgenerator 1, ett kondensatorbatteri 2, en brytare 3, en fördelardosa 4 för distribution av högspänningspulser som genereras vid urladdning av kondensatorbatteriet 2 genom brytaren 3 till en elektrodapplikator 5 och elektroder 6 avsedda att placeras i eller invid det vävnadsområde 7 eller organ 7 hos den patient som är under behandling. Högspänningsgeneratorn 1, kondensatorbatteriet 2, brytaren 3 och fördelardosan 4 är medelst elektriska ledare 33 kopplade i serie med varandra. Mellan fördelardosan 4 och elektrodapplikatorn 5 är anordnat minst en elektrisk ledare 33 och minst en

signalförbindelse 32. Via signalförbindelserna 32 styr fördelardosan 4 spänningssättningen av elektrodapplikatorns elektroder, vilka via de elektriska ledarna 33 sammankopplas med fördelardosan 4 och via den elektriska ledaren 33 med brytaren 3. I en alternativ utföringsform är varje elektrod 6 elektriskt förbunden med brytaren 3 med en elektrisk ledare 33.

Som regel spänningssätter brytaren 4 eller elektrodapplikatorn samtidigt endast två elektroder 6, medan övriga elektroder tillåts anta den potential som bestäms av elektrodens placering i behandlingsområdet. Med begreppet spänningssättning innefattas i detta sammanhang även att en eller flera elektroder är jordade (har nollpotential). Brytaren 4 och/eller elektrodapplikatorn 5 är anordnade för att om så önskas tillåta parvis spänningssättning av samtliga elektroder som appliceras i behandlingsområdet. Det är uppenbart att i vissa utföringsformer är organen anordnade för att vid spänningssättningen tilldela flera elektroder en i huvudsak överensstämmande potential.

Alla enheter är via signalförbindelser 32, vilka i vissa utföringsformer är helt eller delvis trådlösa, anslutna till ett registrerings- och omräkningsorgan 10 med en skärm 10a. I fortsättningen används för registrerings- omräkningsorganet även benämningarna styr- och omräkningsenhet 10 eller dator 10. Datorn 10 utgör ett styr- och kontrollorgan för anordningens funktion.

Med uttrycket elektrodapplikator 5 avses en hållare för elektroderna 6, där hållaren är utformad för att underlätta elektrodernas korrekta applicering till eller i behandlingsområdet.

Datorn inställs som regel för att högspänningspulserna skall innehålla följande data:

repetitionsfrekvens	ca 0.1-10000 per sekund
amplitud	ca 50-6000 V
pulslängd	ca 0.1 - 200 ms
antal pulser	1-2000 per behandling.

Pulserna appliceras före. under eller strax efter strålbehandlingen. Exempel på använd pulsform är fyrkantspuls med pulslängd 0.1 - 2 ms eller exponentiellt avtagande puls med en tidskonstant RC ungefär lika med 0.1 - 2 ms. Vid stora amplituder hos spänningen väljs som regel kortare pulslängder och vice versa.

Högspänningsgeneratorn 1 är som regel anordnad för att avge modulerad växelspänning med en frekvens inom intervallet 40Hz-2MHz och som regel inom intervallet 40Hz-100kHz. I de utföringsformer där högspänningsgeneratorn är anordnad för att avge växelspänning med hög frekvens användes en modulator i stället för kondensatorbatteri och brytare för att bilda korta modulerade högfrekvenspulser med en pulslängd inom området ca 0.1-200 ms.

Som framgår av den i figur 3 visade utföringsformen ingår i anordningen som regel även sensorer 8 avsedda att appliceras på patienten i behandlingsområdet. Sensorerna är via ett detektorinterface 9 förbundna med registrerings- och omräkningsorganet 10. Vid applicering av behandlingspulsen genereras en signal i sensorerna 8 vilken via interfacet 9 överförs till och registreras i datorn 10. Från de uppmätta signalerna beräknar datorn den av pulsen inducerade elektriska fältstyrkan och den elektromotoriska kraften i olika delar av behandlingsområdet 7. Dessa signaler medför att datorn 10 ger signal till högspänningsgeneratorn/kondensatorbatteriet (återkoppling) att justera amplituden på de genererade pulserna så att den förutbestämda fältstyrkan uppnås i behandlingsområdet. Denna kontroll och justering sker kontinuerligt under appliceringen av pulserna.

I figurerna 4a-d visas utföringsformer av elektrodapplikatorer 5 för extern behandling av en patient med elektroderna 6 applicerade i ett begränsat område på patienten och i olika konfigurationer kring det vävnadsområde 7 t ex en tumör 7 som skall behandlas. Figurerna 4a och 4b visar hur man genom korsvis applicering av de elektriska högspänningspulserna till olika kombinationer av två elektroder 6 uppnår att, såsom markeras i figuren av de elektriska

fältstyrkelinjerna, det elektriska fältet passerar genom alla delar av vävnadsområdet 7.

Figur 4c-d visar hur elektroder är utformade med olika stora anliggningsytor för att fältlinjerna skall fokuseras till önskat behandlingsområde. De elektriska högspänningspulserna har vid starten av behandlingen t ex en spänning som justeras efter avståndet mellan elektroderna. Spänningen justeras då enligt sambandet:

Spänning = (konstant) × (avståndet mellan de parvisa elektroderna). Värdet på konstanten varieras efter typ av vävnad och väljs som regel till värden mellan ca 500 - 3000 V/cm.

Sedan behandlingen påbörjats reglerar den nedan beskrivna styrenheten och impedansmätenheten pulsgeneratorns utspänning till värden som medför att eftersträvad elektrisk fältstyrka passerar genom vävnaden.

I figur 5 visas en utföringsform av en elektrodapplikator 5 för intraoperativ behandling och behandling av t ex ytliga tumörnoduler 7. Elektrodapplikatorn har en saxliknande utformning och innehåller två skänklar 12 av elektriskt isolerande material (t.ex. teflon) vilka är rörligt förbundna med varandra i en lagring 11. Skänklarna är försedda med en gripspärr 13. I ena änden av vardera skänkeln 12 är skänklarna försedda med fingergrepp och i sina andra ändar med elektroder 6 som griper om tumörnodulerna 7. Gripspärren 13 fixerar skänklarna 12 i inställt läge. Spänningen på de elektriska högspänningspulserna justeras efter tumörens 7 storlek med hjälp av en i elektrodapplikatorn inbyggd avståndssensor 14 som är ansluten till datorn 10. Spänningen inställs vid starten av behandlingen t ex enligt sambandet:

Spänning = (konstant) × (avståndet mellan de parvisa elektroderna). Värdet på konstanten anpassas efter typ av tumör och väljs som regel inom intervallet ca 500 - 3000 V/cm.

Sedan behandlingen påbörjats reglerar den nedan beskrivna styrenheten och impedansmätenheten pulsgeneratorns utspänning till värden som medför att eftersträvad elektrisk fältstyrka passerar genom vävnaden.

I figur 6a-d visas utföringsformer av elektroder 15.16 och en fixtur 18 för elektroderna där elektroderna och fixturen är lämpade att användas för interstitiell behandling av såväl ytlig som djupliggande vävnad. I figur 6a visas elektroderna 15.16 i två olika utföringsformer nämligen i en utföringsform i vilken elektroderna 15 är nålformade och i en utföringsform i vilken elektroderna 16 är stilettformade. Elektroderna 15.16 är var och en i ett parti 31 närmast sin ena ände försedda med en elektrisk ledare 33 för anslutning till högspänningsgeneratorn 1. Nyss nämnt parti är försett med ett elektriskt isolerande skikt 17 eller en elektriskt isolerad hylsa 17 i vilken elektroden är inskjuten.

Elektroderna appliceras i olika konfigurationer i och omkring den vävnad 7 eller det organ 7 som skall behandlas antingen direkt för fri hand eller med hjälp av en hålförsedd elektrodapplikator (fixtur) 18. Elektrodapplikatorn är som regel utformad för att avlägsnas från elektroderna 15.16 sedan dessa applicerats på patienten. Det blir därigenom möjligt att låta elektroderna sitta kvar i patienten för att användas vid flera efterföljande behandlingstillfällen. Alternativt avlägsnas elektrodapplikatorn tillsammans med elektroderna 15.16 efter varje behandling. Även vid interstitiell behandling förekommer elektroder med olika stora ytor för styrning av det elektriska fältets utbredning.

De delar av elektroderna 15.16 som är avsedda att föras in i patienten för att täcka utbredningen av den vävnad 7 som skall behandlas är t ex tillverkade av rostfritt stål med en kvalitet som överensstämmer med eller motsvarar den som används för injektionsnålar eller är tillverkade eller överdragna av annan vävnadsvänlig metall såsom av ädelmetall t ex guld eller platina. Resterande del av elektroderna bildar en isolerad del 17 med tilledare 33 för högspänningspulserna. Vid användning av mjuka flexibla tilledare placeras elektroden i en grov kanyl 19 som efter elektrodernas applicering i patienten dras tillbaka varvid elektroderna sitter kvar i vävnaden.

I vissa utföringsformer består elektroderna av radioaktiv metall (t.ex. Iridium-192. kobolt-60) eller är de ytbelagda med radioaktiva ämnen (t ex jod-125). I andra utföringsformer är de utformade som rör 20 av inert metall vilka laddas med radioaktivt material (t ex ^{192}Ir. ^{137}Cs. ^{226}Ra) vilket med fördel sker genom användning av en sk. efterladdningapparat 22. Pulserna har en spänning som vid starten av behandlingen t ex bestäms av avståndet mellan elektroderna. Spänningen inställs då enligt sambandet:

Spänning = (konstant) × (avståndet mellan parvisa elektroder). Värdet på konstanten väljs efter typ av tumör som regel inom intervallet ca 500 - 3000 V/cm.

Sedan behandlingen påbörjats reglerar den nedan beskrivna styrenheten och impedansmätenheten pulsgeneratorns utspänning till värden som medför att eftersträvad elektrisk fältstyrka passerar genom vävnaden.

I de tillämpningar där behandling med elektriska fält kombineras med strålbehandling från en strålningskälla som är belägen utanför behandlingsområdet tillförs elektroderna i behandlingsområdet elektriska spänningspulser före. under eller strax efter strålbehandlingen.

I figur 7a-c visas elektroder 24 för behandling av vävnad åtkomlig via t ex stora kärl. eller via kroppskaviteter t ex luftvägar. urinvägar och mag-tarmkanal. Elektroderna är anordnade på ytan av en cylinderliknande elektrodapplikator 23 av isolerande material 17. I vissa utföringsformer är elektroderna så utformade att de förs in i vävnaden genom kanaler 25 i applikatorn 23 manövrerade av en distanskontroll. Som framgår av fig 7c mynnar i den i föregående mening angivna utföringsformen kanalerna 25 i elektrodapplikatorns mantelyta varigenom elektroderna 24 vid sin förflyttning styrs in i vävnad som omger elektrodapplikatorn. I vissa utföringsformer är applikatorn anordnad för att tillföras radioaktiva preparat. varigenom applikatorn även bildar ett strålningsorgan. Applikatorn är anordnad för att tillföras de radioaktiva preparaten manuellt eller medelst en efterladdningsapparat 22. De elektriska högspänningspulsernas spänning justeras under behandlingen.

Fältlinjerna i figur 7a indikerar utbredningen av de elektriska fältlinjerna i vävnaden.

För intrakavitär behandling av vävnad i olika oregelbundet formade kroppskaviteter (t ex munhåla, luftvägar, matstrupe, mage, uterus, urinblåsa, urinledare, ändtarm) appliceras elektrodapplikatorer 23, som framgår av fig 7a-c, speciellt utformade efter kavitetens form med elektroder applicerade på ytan 24 eller alternativt utformade som nålar som genom kanaler 25 föres in i vävnaden med distanskontroll. Dessa applikatorer är lämpade att användas t.ex. för behandling av lungcancer, levertumörer, njurtumörer och tumörer i mag-tarmkanalen med reducerad absorberad dos för att minska bieffekter av strålbehandlingen i normalvävnad. Prostatacancer behandlas med applikatorer applicerade via rectum och urinledare. Dessa applikatorer är i vissa utföringsformer utformade för att laddas med radioaktiva källor eller radioaktivt material 21 manuellt eller med efterladdningsapparat 22.

I figur 8 visas anordning för kombinationsbehandling med antitumorala läkemedel där elektroden 6 är belagd med ett lager 28 av porös metall, glas, keramik, inert plast eller annan polymer vilken innehåller antitumorala läkemedel 29 (t ex bleomycin, platinol, taxol, monoklonala antikroppar), genetiskt material (kromosomer, DNA) eller radioaktiva substanser (t ex jod-125, Augerelektronemitterare) 29. Denna typ av elektrod är väl lämpad att användas vid strålningsterapi eftersom den höga elektriska fältstyrkan ökar tumörcellernas genomsläpplighet för ovannämnda substanser och därigenom ökar den antitumorella effekten.

Fig 9a-e visar exempel på pulsformer hos de spänningspulser som parvis påläggs elektroderna 6,15,16,24. I figurerna representera pulsens höjd spänningen mellan två elektroder. Pulsens bredd representerar pulsens längd. Figurerna 9a och 9c visar exempel på fyrkantspulser, fig 9b och 9d exempel på pulser vars spänning avtar med tiden och fig 9e pulser av växelspänning. Fig 9c och 9d visar spänningspulser där, motsvarande vad som gäller för växelspänning,

elektroderna växelvis har den högsta spänningen varigenom motsvarande ändring sker av det elektriska fältet mellan elektroderna.

I det i fig 10 visade blockschemat ingår de ovan beskrivna elektroderna 6.15.16.24, spänningsgeneratorn 1, styr- och omräkningsorganet 10 även tidigare benämnt datorn och en impedansmätenhet 50. Spänningsgeneratorn, datorn, elektroderna och impedansmätenheten är förbundna med varandra med elektriska ledare för spänningssättning av elektroderna och för överföring av signaler. Det är uppenbart att i vissa utföringsformer åtminstone en del av signalförbindelserna är utformade som trådlösa förbindelser.

Fig 11a visar den principiella strukturen för levande vävnad medan fig 11b visar ett elektrisk principschema för den elektriska strukturen hos vävnaden. Motsvarigheterna mellan resistanserna och kapacitansen i det elektriska schemat och i vävnaden framgår av komponenternas beteckningar och av den fortsatta beskrivningen.

Fig 12 visar den principiella elektriska strukturen hos en pulsgenerator 1 tidigare även benämnd högspänningsgenerator. Figuren visar hur vävnadens impedans $Z_{vävnad}$ via elektroderna 6.15.16.24 är seriekopplad med pulsgeneratorns inre impedans $Z_{generator}$. Med U avses pulsgeneratorns elektromotoriska kraft (EMK).

Det är uppenbart att de ovan beskrivna mekaniska enheterna i vissa utföringsformer av uppfinningen bildar från varandra separerade mekaniska enheter som är sammankopplade med varandra medelst elektriska ledare och signalförbindelser medan i andra utföringsformer några av enheterna eller alla enheterna med undantag för elektrodapplikatorn och elektroderna bildar en med spänningsgeneratorn, impedansmätenheten eller datorn sammanhållen mekanisk enhet.

Som framgår av den ovanstående beskrivningen avser uppfinningen en anordning för högvoltsimpulsterapi (HVIT) med detektering av behandlingseffekten. I anordningen ingår en impedansmätenhet som vid behandling av vävnad eller organ används för att mäta vävnadens elektriska impedans. Impedansmätenheten är som regel anordnad för att mäta vävnadens impedans vid minst en frekvens. Vanligen är impedansmätenheten anordnad att mäta vävnadens impedans inom ett frekvens-

område t ex inom området 10 Hz till 10 MHz. Med hjälp av en matematisk algoritm beräknas en teststorhet vars värde är ett mått på behandlingseffekten.

Spänningen över vävnaden blir i enlighet med vad som visas i figur 12:

$$U_{vävnad} = U_{generator} * Z_{vävnad} / (Z_{vävnad} + Z_{generator})$$

Vävnadens impedans varierar mycket kraftigt beroende på den behandlade vävnadens cellstruktur och uppbyggnad, den kringliggande vävnadens beskaffenhet samt mängden kroppsvätskor som finns i och kring det behandlade området. Eftersom generatorns utgångsimpedans inte är liten i förhållande till vävnadens impedans kommer utspänningen att variera kraftigt beroende på var och hur applikatorn placeras. Det har visat sig vid praktiska försök att även om en applikator placeras på samma ställe, märkt med en färg på kroppen, kommer impedansen att variera kraftigt från gång till gång beroende på små skillnader i placering och kontaktimpedans samt skillnader i vätskemängd och beskaffenhet hos vävnaden.

För att kunna förutsäga den verkliga pulsspänningen från pulsgeneratorn måste vävnadens impedans vid varje tillfälle vara känd. Endast om man justerar utspänningen från generatorn med utgångspunkt från generatorns utgångsimpedans och den aktuella vävnadens impedans uppnår man en förutsägbar och konstant effekt. Enligt uppfinningen ingår i anordningen organ för mätning av impedansen hos den behandlade vävnaden och organ för att använda denna information för styrning av pulsgeneratorns utspänning så att önskad fältstyrka alltid uppnås i vävnaden.

Fig 10 illustrerar ett sådant system. En styrenhet ingår i anordningen och mäter med hjälp av impedansmätenheten vävnadens impedans. Styrenheten justerar utspänningen från generatorn så att önskad fältstyrka uppnås. På styrenheten, som t ex är en persondator, ställer man in önskad fältstyrk, varefter styrenheten mäter impedansen i vävnaden och räknar ut erforderlig pulsspänning från generatorn. När sedan en puls appliceras kommer fältstyrkan alltid att vara konstant eftersom styrenheten hela tiden mäter och justerar spänningen från generatorn innan pulsen genereras.

Med systemet i fig 10 uppnås den eftersträvade effekten dvs att hålla en konstant utspänning från pulsgeneratorn oberoende av impedansen i vävnaden. Det visar sig också att ett system enligt fig 10 lämpar sig utmärkt för att mäta och bedöma det behandlingsresultat man uppnår vid HVIT. Genom att mäta impedans och utföra analys av impedansförändring i vävnaden efter att en puls pålagts ges underlag för att bedöma när behandlingen är fullbordad och inga fler pulser behövs eller ger ytterligare positiv effekt. Denna metod bygger på den vävnadsmodell som visas i fig 11a,b.

Impedansen hos vävnad består i huvudsak av tre komponenter, resistansen hos den extracellulära vätskan, resistansen hos den intracellulära vätskan och den kapacitans som bildas genom cellmembranens likströmsisolerande verkan. I modellen har vi slagit samman cellkärnans impedanspåverkan med resistansen hos den intracellulära vätskan. Vid låga frekvenser kommer endast ström att flyta genom den extracellulära vätskan och impedansen bestäms i huvudsak av R_{ev}. Vid medelhöga frekvenser kommer cellmembranens kapacitans, C_{cm} tillsammans med den intracellulära vätskans resistans, R_{iv}, att börja påverka impedansen. Vid höga frekvenser kommer i huvudsak komponenterna R_{ev} och R_{iv} att påverka vävnadens impedans. Således kommer man att få ett frekvensberoende hos vävnadens impedans som till stor del beror av cellmembranens tjocklek och cellernas utformning. Vid låga frekvenser är impedansen ungefär R_{ev} och vid höga frekvenser $R_{ev}//R_{iv}$. Tecknet // används för att ange att R_{ev} är parallellkopplad med R_{iv}.

$$Z_{vävnad} = R_{ev} // (R_{iv} + C_{cm})$$

Eftersom behandlingen med elektriska fält syftar till att permeabilisera eller helt förstöra cellmembranen får man genom mätning av förändringen hos C_{cm} klarhet i om behandlingen är fullbordad eller ej. När samtliga cellmembran i vävnaden är förstörda sker ingen förändring av C_{cm} längre och vävnaden är färdigbehandlad.

Tabell 1 nedan illustrerar en uppsättning impedansmätningar som tagits under behandling av råtta med tumör.

Tabell 1 Uppmätt vävnadsimpedans i ohm hos råtta med tumör

Frekvens/Pulser	0 pulser	16 pulser	32 pulser	48 pulser	64 pulser
10 Hz	232.24	160.12	160.36	172.53	179.3
15 Hz	229.42	157.76	151.48	163.37	159.61
20 Hz	200.28	145.46	138.84	148.89	141.78
30 Hz	173.9	134.11	127.56	132.16	125.87
50 Hz	153.7	122.75	116.44	120	112.29
70 Hz	144.46	116.39	110.38	136.26	105.58
100 Hz	137.64	110.69	105.13	105.47	100.31
150 Hz	130.68	104.86	99.79	99.71	95.35
200 Hz	125.81	100.97	96.31	96.23	92.26
300 Hz	120.3	96.27	92.06	92.19	88.73
500 Hz	113.96	91.09	87.49	87.84	84.91
700 Hz	109.83	87.88	84.68	85.16	82.6
1000 Hz	105.88	85.03	82.2	83.03	80.62
1500 Hz	101.99	82.12	79.71	81.84	78.59
2000 Hz	99.34	80.27	78.02	79.54	77.69
3000 Hz	96.12	77.98	76.06	77.18	75.72
5000 Hz	92.28	75.4	73.81	74.85	73.71
7000 Hz	89.72	73.85	72.41	73.86	72.54
10000 Hz	87.38	72.45	71.14	73.52	71.43
15000 Hz	84.91	70.91	69.71	72.53	70.15
20000 Hz	83.18	69.75	68.62	71.51	69.17
30000 Hz	80.8	68.23	67.14	69.81	67.8
50000 Hz	77.73	66.26	65.28	68.24	65.97
70000 Hz	75.62	64.79	63.9	66.67	64.65
100000 Hz	73.01	63.01	62.11	64.62	62.93
150000 Hz	70.42	61.05	60.3	64.06	61.19
200000 Hz	68.3	59.37	58.76	61.93	59.65

Av tabell 1 framgår att impedansen minskar vid låga och medelhöga frekvenser efter behandling med pulser. Minskningen sker i första hand efter de inledande 16 pulserna och förändringen avtar snabbt därefter. Råttan är alltså väsentligen färdigbehandlad redan efter de första 16 pulserna och vidare behandling efter 32 eller 48 pulser ger ingen större förändring av C_{cm}. Mätdatat i tabell 1 indikerar att behandlingen är fullbordad efter 32 pulser. För att bekräfta denna bedömning har uppmätta mätvärden upptagits och behandlats såsom beskrivs nedan.

Tabell 2 visar impedansförändringen i procent vid olika frekvenser efter det att elektriska fält genererade av 16 spänningspulser passerat genom vävnaden. I tabellen anges i procent den ändring av impedansen som varje gång uppstått när en serie av elektriska fält genererade av spänningspulserna har passerat genom vävnaden.

Tabell 2

Impedansförändring i procent efter behandling med 16 pulser åt gången

Frekvens/Pulser	16 pulser	32 pulser	48 pulser	64 pulser
10 Hz	-31.05408	0.1033414	5.2402687	2.9150878
15 Hz	-31.23529	-2.737338	5.1826345	-1.638916
20 Hz	-27.37168	-3.305372	5.0179748	-3.55003
30 Hz	-22.88097	-3.766532	2.6451984	-3.617021
50 Hz	-20.13663	-4.1054	2.3162004	-5.016265
70 Hz	-19.43098	-4.160321	17.914994	-21.23771
100 Hz	-19.58006	-4.039523	0.2470212	-3.74891
150 Hz	-19.75819	-3.879706	-0.061218	-3.336394
200 Hz	-19.74406	-3.703998	-0.063588	-3.155552
300 Hz	-19.97506	-3.499584	0.1080632	-2.876143
500 Hz	-20.06845	-3.159003	0.3071253	-2.571078
700 Hz	-19.98543	-2.913594	0.4370391	-2.330875
1000 Hz	-19.6921	-2.672837	0.7839063	-2.276162
1500 Hz	-19.4823	-2.362977	2.08844	-3.186587
2000 Hz	-19.1967	-2.264949	1.5300987	-1.862291
3000 Hz	-18.87224	-1.997503	1.1652102	-1.518935
5000 Hz	-18.29215	-1.723017	1.1270048	-1.235371
7000 Hz	-17.68836	-1.604993	1.6161391	-1.471244
10000 Hz	-17.08629	-1.499199	2.7237354	-2.391852
15000 Hz	-16.48805	-1.413261	3.3211636	-2.802968
20000 Hz	-16.14571	-1.3585	3.4743929	-2.813176
30000 Hz	-15.55693	-1.34901	3.3044554	-2.487624
50000 Hz	-14.75621	-1.260774	3.8080535	-2.920365
70000 Hz	-14.32161	-1.176937	3.6630521	-2.671251
100000 Hz	-13.69675	-1.232708	3.4378852	-2.314751
150000 Hz	-13.30588	-1.065038	5.3393922	-4.075547
200000 Hz	-13.07467	-0.893119	4.6412884	-3.338214

I tabellens huvud anges det ackumulerade antalet pulser av elektriska fält som passerat genom vävnaden. Vid varje behandlingstillfälle har en serie av 16 pulser passerat genom vävnaden. Vad som i detta stycke anges för tabellhuvudet i tabell 2 gäller även för de nedan använda tabellhuvudena i tabell 3 och 4.

Av tabell 2 framgår på samma sätt som av tabell 1 att behandlingen kan avbrytas efter 32 pulser eftersom impedansförändringen avtar kraftigt. I tabell 3 nedan visas medelvärdet av impedansförändringen efter olika antal pulser. Medelvärdet är bildat av samtliga uppmätta frekvenser mellan 10Hz och 200kHz. I tabell 3 ser man tydligt att den största impedansförändringen sker efter de första 16 pulserna och endast en ringa förändring sker vid vidare behandling.

Tabell 3 Successiv förändring i procent av impedansvärden vid frekvenser mellan 10Hz - 200 kHz

16 pulser	32 pulser	48 pulser	64 pulser
-19.9568	-2.424687	3.1275358	-3.366544

I tabell 4 är vid medelvärdesbildningen frekvenser under 100 Hz och frekvenser över 10kHz bortvalda. Genom att ta bort de lägsta frekvenserna från medelvärdet förhindrar man att felaktiga impedansvärden på grund av störningar från kroppens motoriska system påverkar resultatet. De högsta frekvenserna tas bort eftersom impedansändringen vid dessa är mindre när C_{cm} ändras och därför inte bidrar till en bättre bild av behandlingsresultatet.

Tabell 4 Successiv förändring i procent av impedansvärden vid frekvenser mellan 100 Hz - 10kHz

16 pulser	32 pulser	48 pulser	64 pulser
-20.78512	-2.943407	1.0007481	-2.663449

Genom att låta styrenheten i figur 10 matematiskt behandla och presentera det uppmätta behandlingsresultatet såsom beskrivits ovan erhålls en anordning som uppfyller önskemålen att vid behandlingen styra det elektriska fältets styrka. för att få underlag för att avbryta behandlingen vid rätt tillfälle och för att kunna tolka det direkta utfallet av behandlingen med det elektriska fältet.

Av ovanstående beskrivning framgår att i en mycket enkel tillämpning av uppfinning bestäms vävnadens impedans vid endast en frekvens. Därvid väljs en medelhög frekvens t ex 15kHz. Pulsgeneratorns inre impedans införs i datorn som ett fast värde varigenom vävnadens impedans bestäms genom en räkneoperation

motsvarande den som beskrivits ovan. Vid tillämpningar av uppfinningen används dock som regel många frekvenser för att eliminera risker för ev störningar som kan påverka mätresultatet.

Det i fig 10 visade systemet innefattar organ för att justera pulsspänningen och dess frekvensinnehåll så att det elektriska fältet i den behandlade vävnaden alltid är konstant oberoende av impedans- eller resistansändringar hos vävnaden. Organen ger även underlag för bedömning av den uppnådda behandlingseffekten därigenom att den har en uppbyggnad som gör det möjligt att presentera t ex enkla förståeliga värden och grafer vilka genom matematiska operationer har extraherats från uppmätta impedans- eller resistansdata.

Vid tillämpning av uppfinningen i den utföringsform där en strålningssändare används bildar strålningssändaren och elektroderna i vissa utföringsformer tillsammans med elektrodapplikatorn och impedansmätenheten en sammanhållen mekanisk enhet. Denna har en utformning som gör det möjligt att i ett begränsat område hos en människa eller ett djur applicera såväl strålningssändaren som elektroderna i positioner där den joniserande strålningen är riktad mot den vävnad som behandlas och där elektroderna har positioner i vilka elektriska fält mellan dessa passerar genom vävnaden. I andra utföringsformer utgör organen separata mekaniska delar som tillsammans och i förekommande fall tillfälligt eller undre längre tid bildar ett system av organ med en sammansättning motsvarande den som ovan angivits för anordningen 40.

Ovanstående detaljbeskrivning har endast refererat till ett begränsat antal utföringsformer av uppfinningen, men det inses lätt av fackmannen att uppfinningen inrymmer ett stort antal utföringsformer inom ramen för de efterföljande patentkraven.

SM 245.3/2

PATENTKRAV

1. Anordning (60) för att styra storleken på, formen hos och/eller varaktigheten hos elektriska fält som genereras av en spänningsgenerator (1) mellan i anordningen ingående elektroder (6,15,16,24) eller mellan till anordningen anslutna elektroder (6,15,16,24), där anordningen innefattar organ (4,5) för fördelning av spänningspulserna till elektroderna (6,15,16,24) för bildandet av de elektriska fälten och där elektroderna är utformade för att fästas vid ett begränsat område hos en människa eller hos ett djur eller är utformade för att införas i sagda område, k ä n n e t e c k n a d därav, att en i anordningen ingående impedansmätenhet (50) är anordnad för att vid behandling av vävnad eller organ intill eller i sagda område bestämma impedansen och/eller resistansen mellan sagda elektroder och att en styr- och omräkningsenhet (10) ingår i anordningen eller är kopplad till denna för att före varje spänningspuls eller kedja av spänningspulser och baserat på den uppmätta impedansen och/eller resistansen styra storleken på, antalet av, formen hos och/eller varaktigheten för de spänningar som påläggs elektroderna.

2. Anordning enligt krav 1, k ä n n e t e c k n a d därav, att styr- och omräkningsenheten (10) innefattar en bildskärm, att styr- och omräkningsenheten är anordnad för att före starten av spänningsgeneratorns (1) generering av en puls eller kedja av pulser på bildskärmen (10a) visa av styr- och omräkningsenheten beräknad utformning av pulsen eller kedjan av pulser och att i styr- och omräkningsenheten ingår organ för manuell eller automatisk acceptans av sagda beräknade utformning.

3. Anordning enligt krav 1 eller 2, k ä n n e t e c k n a d därav, att elektroderna (6,15,16,24) är gemensamma för impedansmätenheten (50) och för organet (4,5) för avgivandet av spänningspulserna eller att separata elektroder (4,5) är anordnade för impedansmätenheten och organet för avgivande av spänningspulser.

4. Anordning enligt något av föregående krav, k ä n n e t e c k n a d därav, att elektroderna (6,15,16,24) är anordnade för att vid behandlingen vara placerade i ett begränsat område i en människa eller i ett djur eller i positioner medförande att det elektriska fältet passerar genom sagda område.

5. Anordning enligt något av föregående krav, k ä n n e t e c k n a d därav, att i anordningen ingår organ (34) för tillförande av terapeutiska substanser, genetiskt material och/eller joniserande strålning till sagda begränsade område hos en människa eller hos ett djur eller att anordningen är utformad för att samverka med ett sådant organ (34).

6. Anordning enligt något av föregående krav, k ä n n e t e c k n a d därav, att anordningen innefattar sensorer (8) för detektering av elektriska fält bildade av elektroderna (6,15,16,24) och att sensorerna är anslutna till ett registrerings- och omräkningsorgan (10) för beräkning av den elektriska fältstyrkans storlek i behandlingsområdet och att för reglering av amplituden hos de på elektroderna pålagda spänningspulserna registrerings- och omräkningsorganet (10) är anslutet till högspänningsgeneratorn (1) och/eller till organ (2,3,4) inkopplade mellan högspänningsgeneratorn (1) och elektroderna (6,15,16,24).

7. Anordning enligt något av föregående krav, k ä n n e t e c k n a d därav, att elektroderna (6) är anordnade för att exiteras växelvis och endast två åt gången.

8. Anordning enligt något av föregående krav, k ä n n e t e c k n a d därav, att i anordningen ingår sensorer (14) för detektering av avståndet mellan elektroderna (6) hos varje par av exiterade elektroder och att registrerings- och omräkningsorganet (10) innefattar organ för att baserat på avståndet mellan elektroderna inställa spänningen mellan elektroderna (6) hos varje par av exiterade elektroder.

9. Anordning enligt något av föregående krav, k ä n n e t e c k n a d därav, att elektroderna (6) är utformade som nålar (15) eller stiletter (16).

10. Anordning enligt något av föregående krav, k ä n n e t e c k n a d därav, att elektroderna (6,15,16,24) helt omsluts av ett elektriskt isolerande skikt (17) eller har ett elektriskt isolerande skikt som åtminstone lämnar en elektriskt ledande spets hos elektroderna oisolerad.

11. Anordning enligt något av föregående krav, k ä n n e t e c k n a d därav, att en elektrodapplikator (5,23) är anordnad för att åtminstone temporärt fixera elektroderna före elektrodernas placering på eller i behandlingsområdet.

12. Anordning enligt krav 11, k ä n n e t e c k n a d därav, att elektrodapplikatorn (23) har en storlek och form som är anpassad efter det kärl, kroppsöppning eller kroppskavitet där den skall placeras.

13. Anordning enligt krav 11, k ä n n e t e c k n a d därav, att elektrodapplikatorn (5) innefattar en fixtur (18) för fixering av elektroderna (15,16) i ett fixt mönster.

14. Anordning enligt krav 11, k ä n n e t e c k n a d därav, att fixturen (18) är försedd med ett antal hål för placering av elektroderna i ett vid varje behandlingstillfälle önskat mönster.

15. Anordning enligt krav 11, k ä n n e t e c k n a d därav, att elektrodapplikatorn (23) är anordnad med elektroder (24) placerade på applikatorns yta eller att elektroderna (24) är placerade i kanaler (25) mynnande i öppningar i applikatorns yta och medelst distanskontroll förflyttbara i kanalerna och åtminstone delvis ut genom öppningarna för att föras in i vävnaden kring applikatorn.

16. Anordning enligt något av kraven 1-10. k ä n n e t e c k n a d därav, att anordningen innefattar minst en kanyl (19) var och en anordnad för att temporärt innesluta en elektrod.

17. Anordning enligt något av föregående krav, k ä n n e t e c k n a d därav, att elektroderna (6,15,16,24) består av radioaktivt material eller är utformade med håligheter för upptagande av radioaktiva preparat (21).

18. Anordning enligt något av föregående krav, k ä n n e t e c k n a d därav, att elektroderna (6,15,16,24) är belagda med ett skikt (27) av poröst material för upptagande av terapeutiska substanser (28).

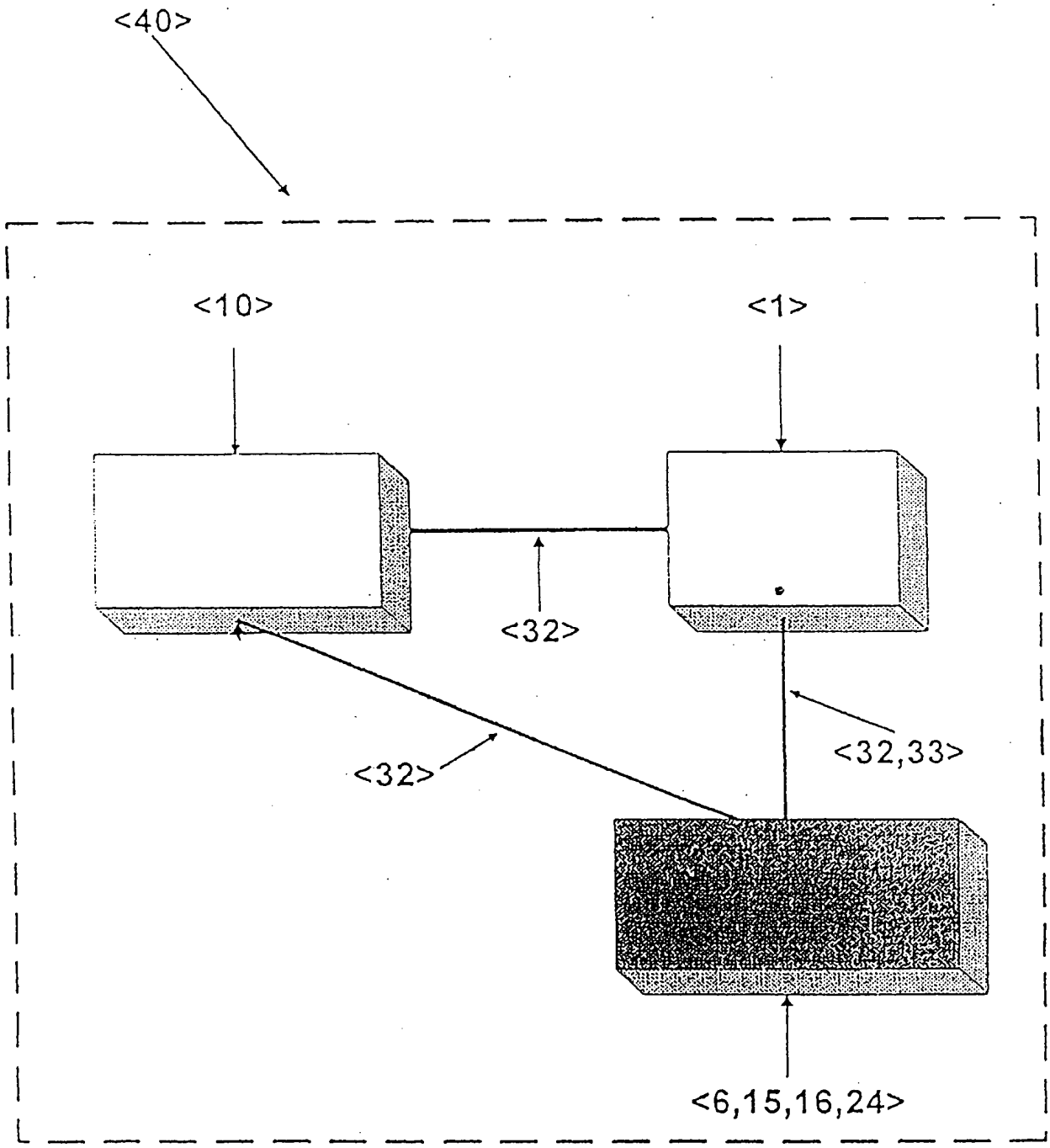
SAMMANFATTNING

I en anordning (60) enligt uppfinningen ingår en spänningsgenerator (1) för generering av kortvariga spänningspulser för spänningssättning av i anordningen ingående elektroder (6,15,16,24) och en mätenhet (50) som är kopplad till elektroderna. Dessa är utformade för att fästas vid eller införas i vävnad i ett begränsat område hos en människa eller ett djur för att mellan sig bilda elektriska fält i vävnaden. Mätenheten (50) är anordnad för att bestämma impedansen mellan elektroderna vilken i huvudsak bestäms av de elektriska egenskaperna hos den vävnad som befinner sig mellan elektroderna. Ett registrerings- och beräkningsorgan (10) bildar en styrenhet som baserat på den av mätenheten bestämda impedansen styr spänningsgeneratorns utspänning så att det elektriska fält som bildas i vävnaden alltid har ett förutbestämt värde.

Behandlingen med det elektriska fältet åstadkommer en perforering av cellmembran i vävnaden vilka därigenom tillåter passage av till kroppen tillförda ämnen (t ex cytostatika eller genetiskt material).

Fig 10

Fig. 1



SUBSTITUTE SHEET

Fig. 2

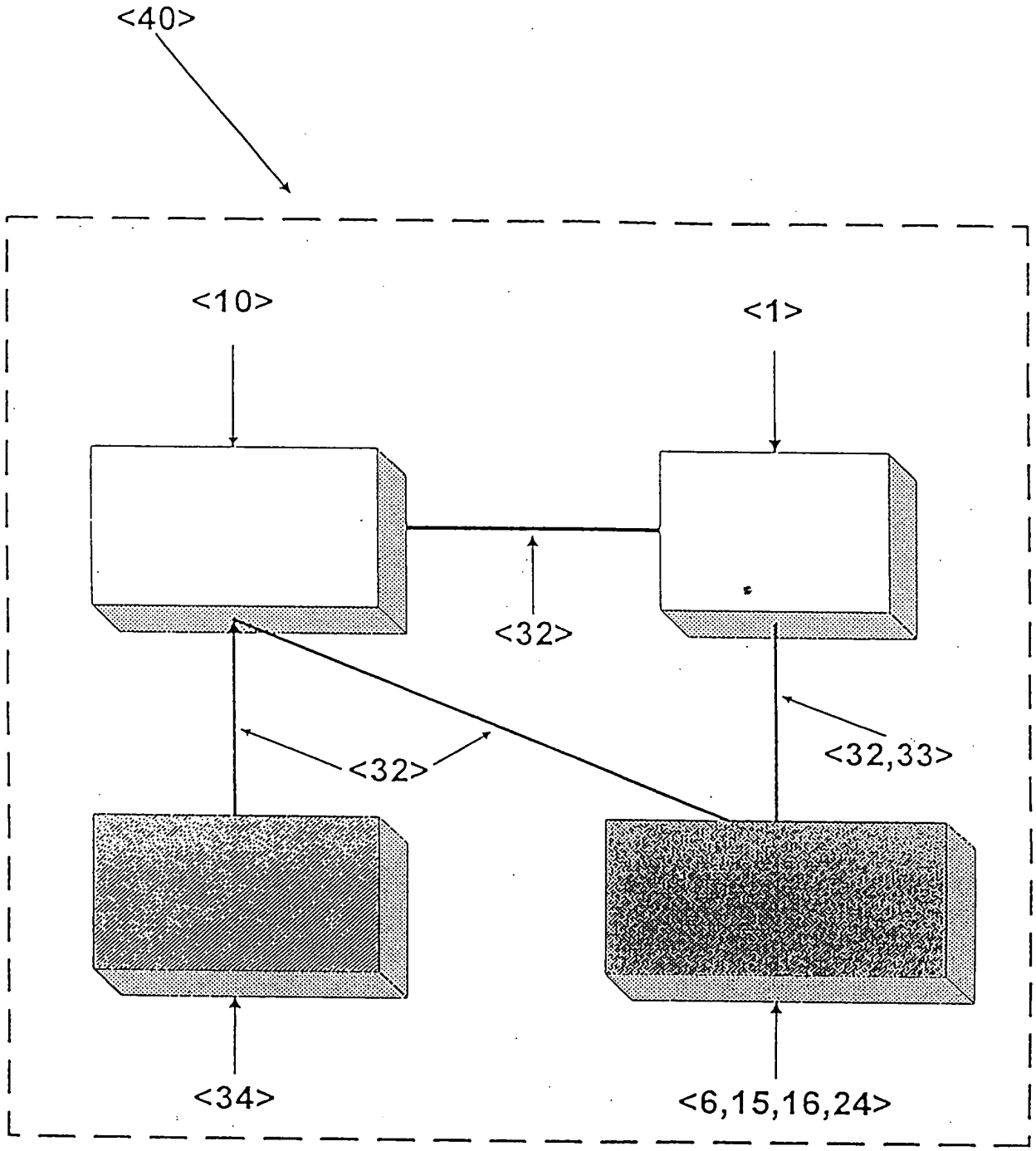


Fig. 3

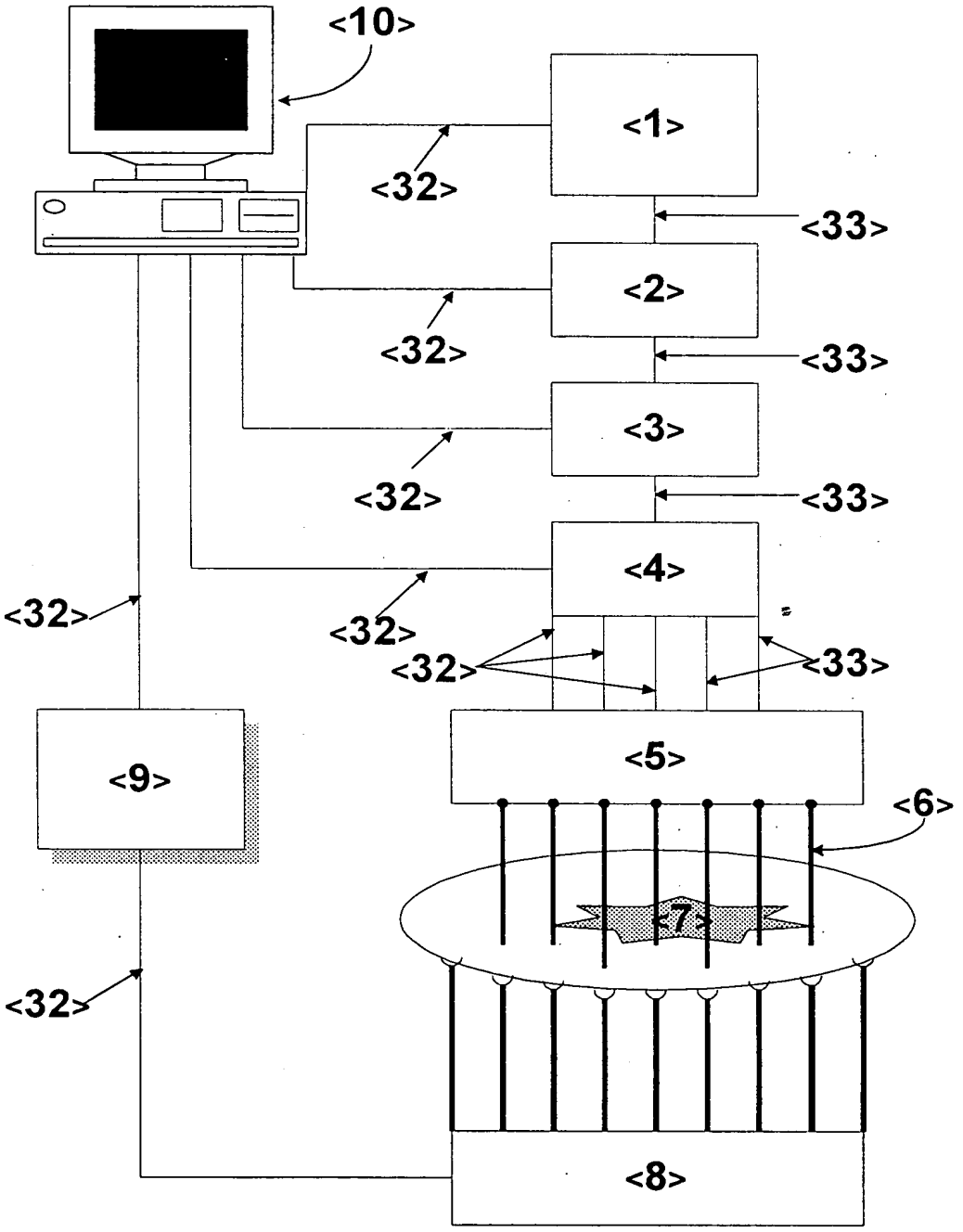
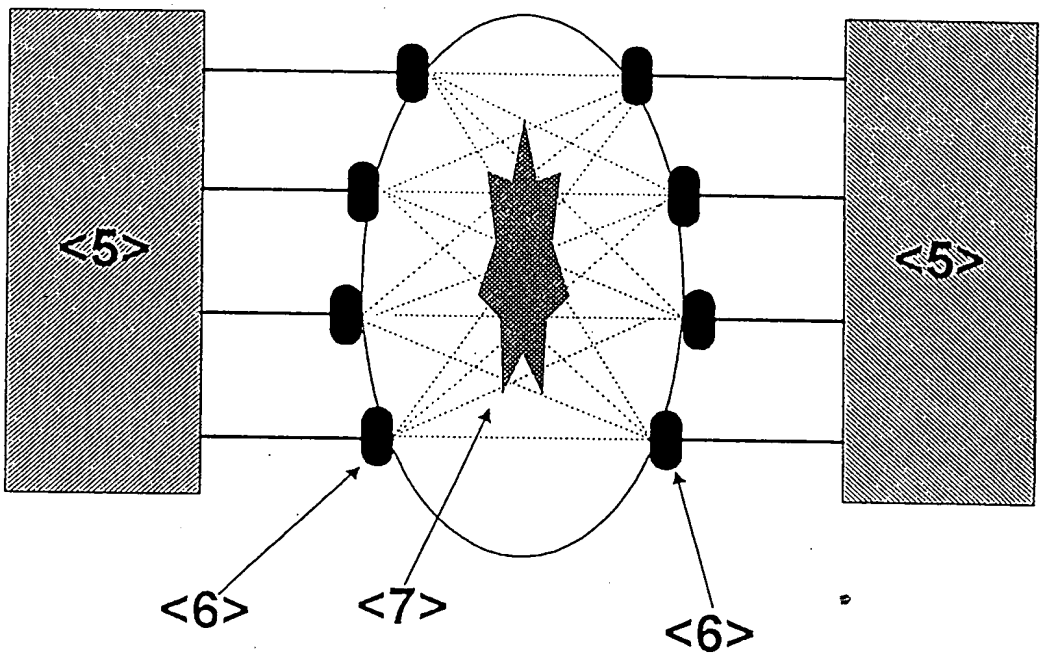


Fig. 4 a,b



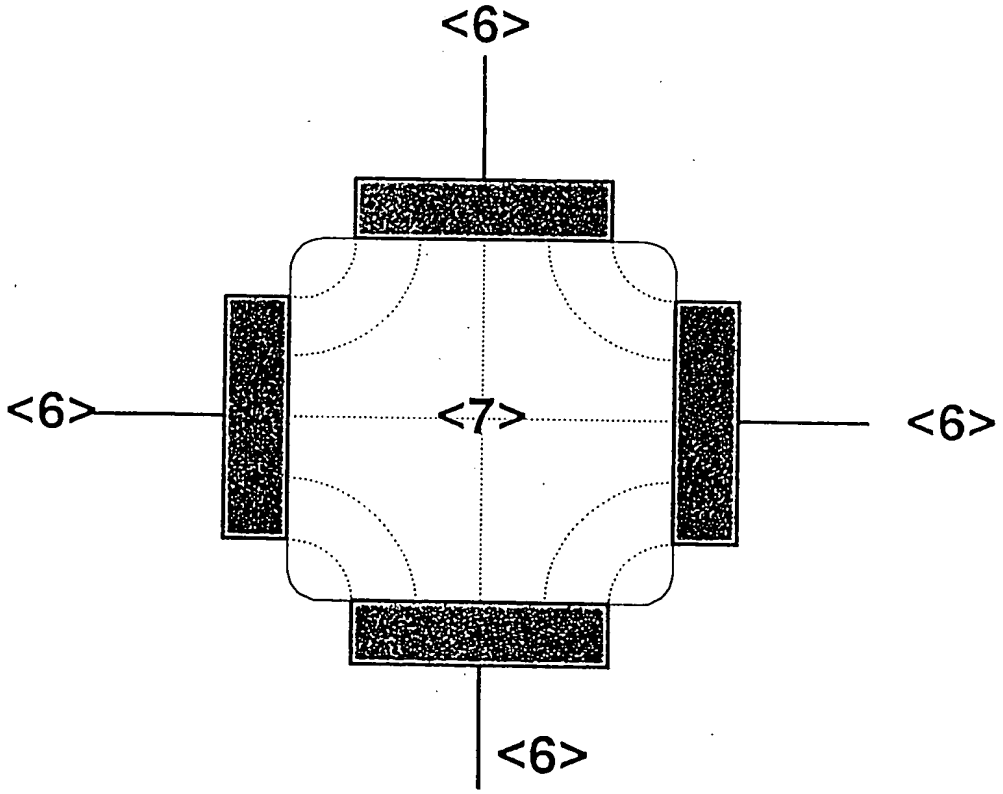


Fig. 4 c,d

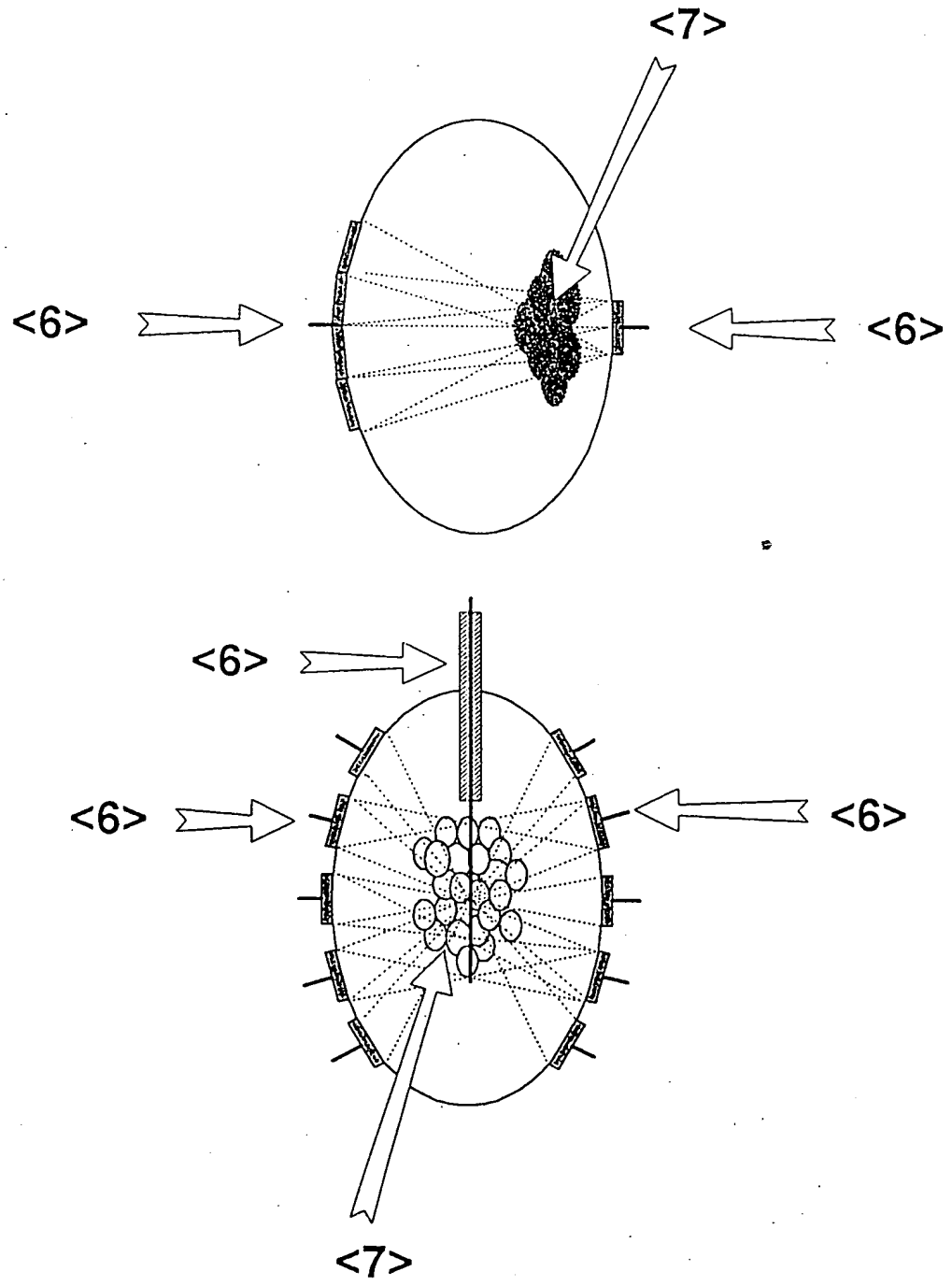
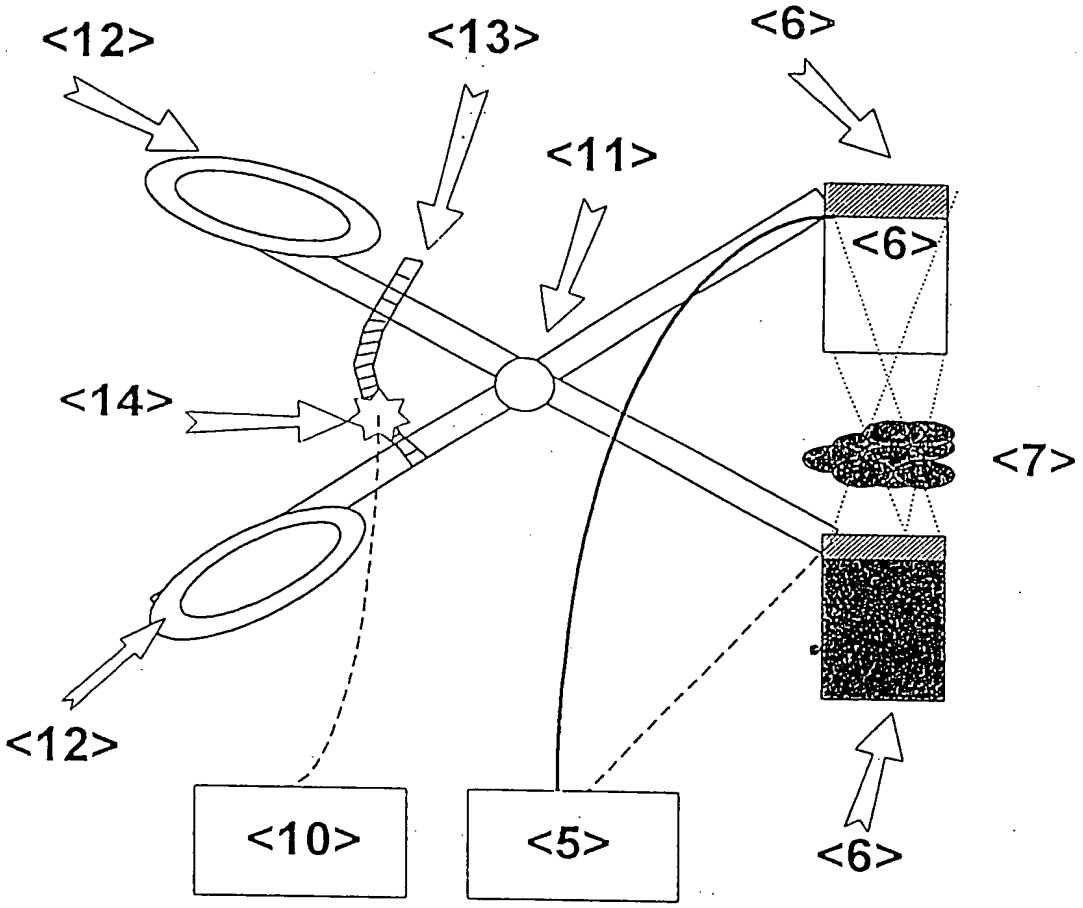


Fig. 5



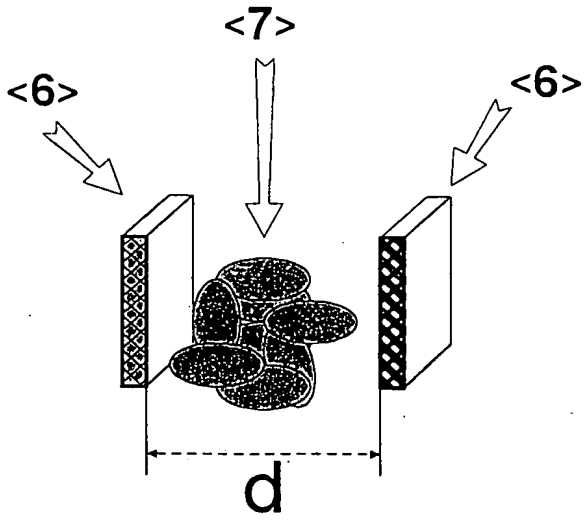


Fig. 6 a

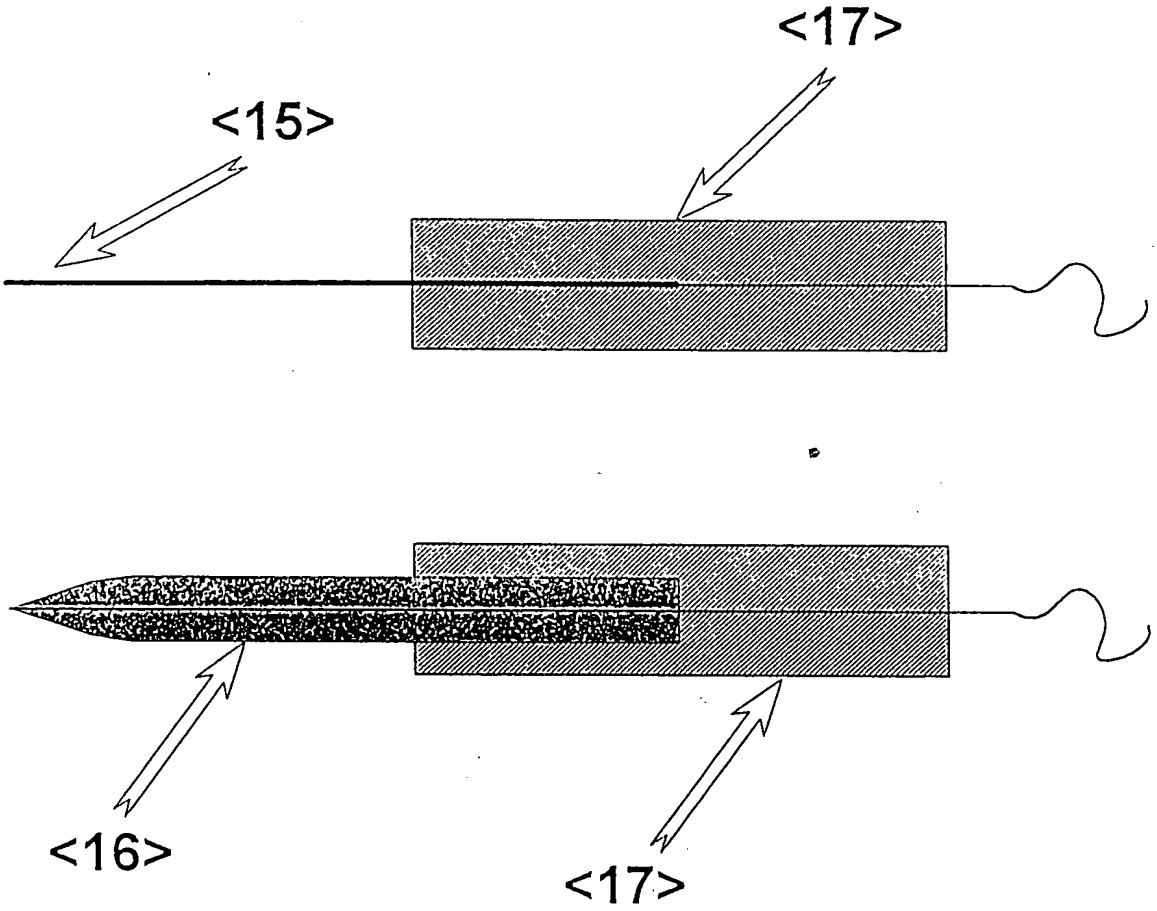


Fig. 6 b

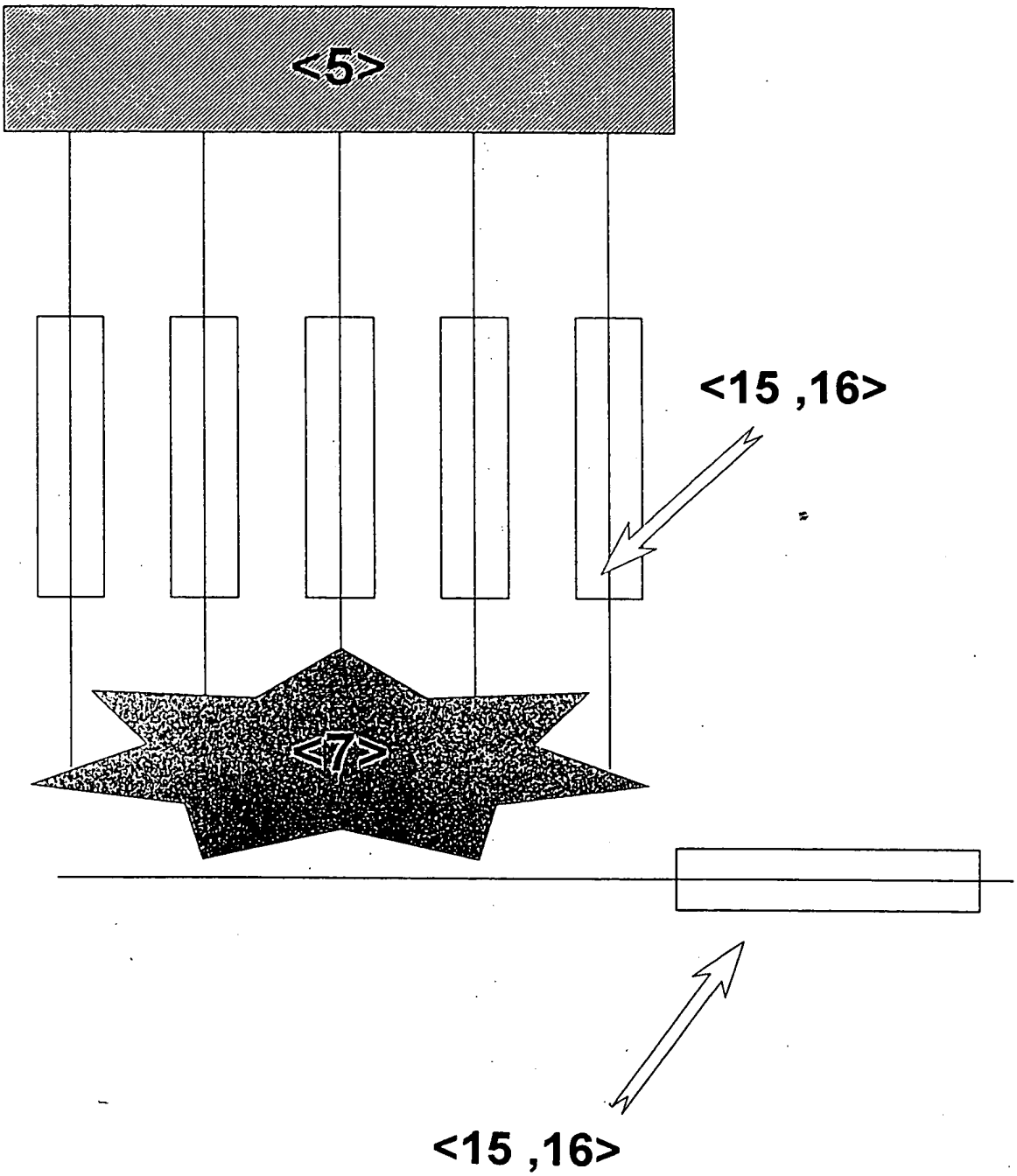


Fig. 6 c

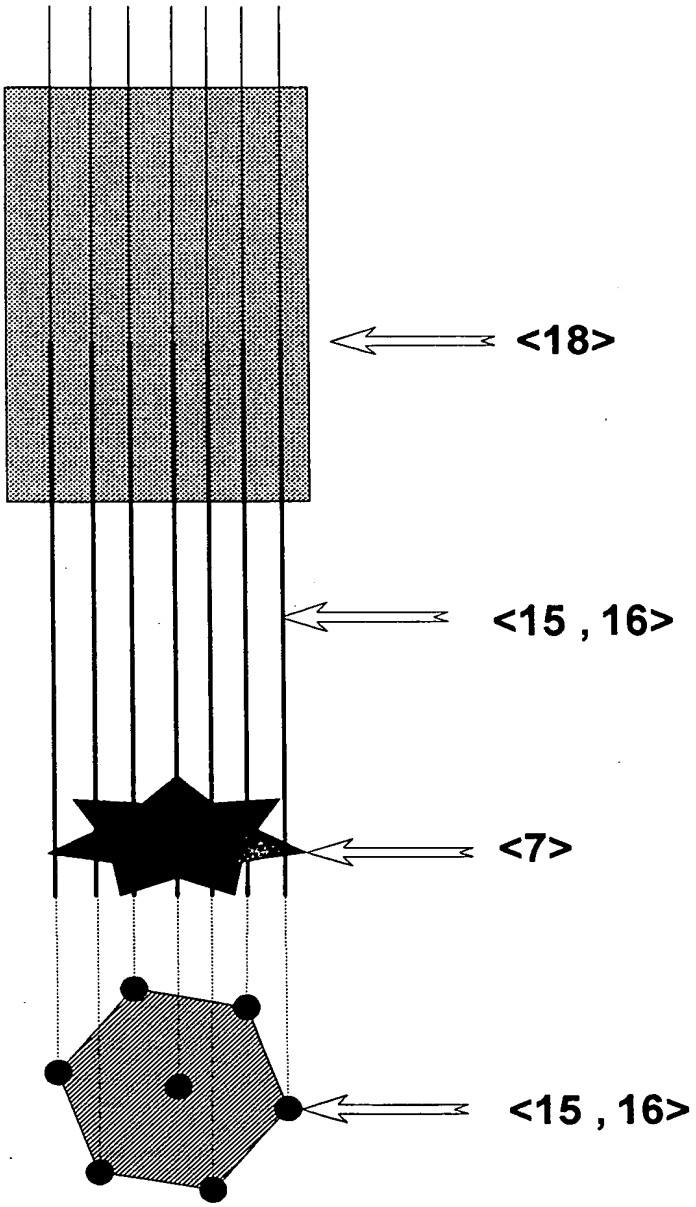
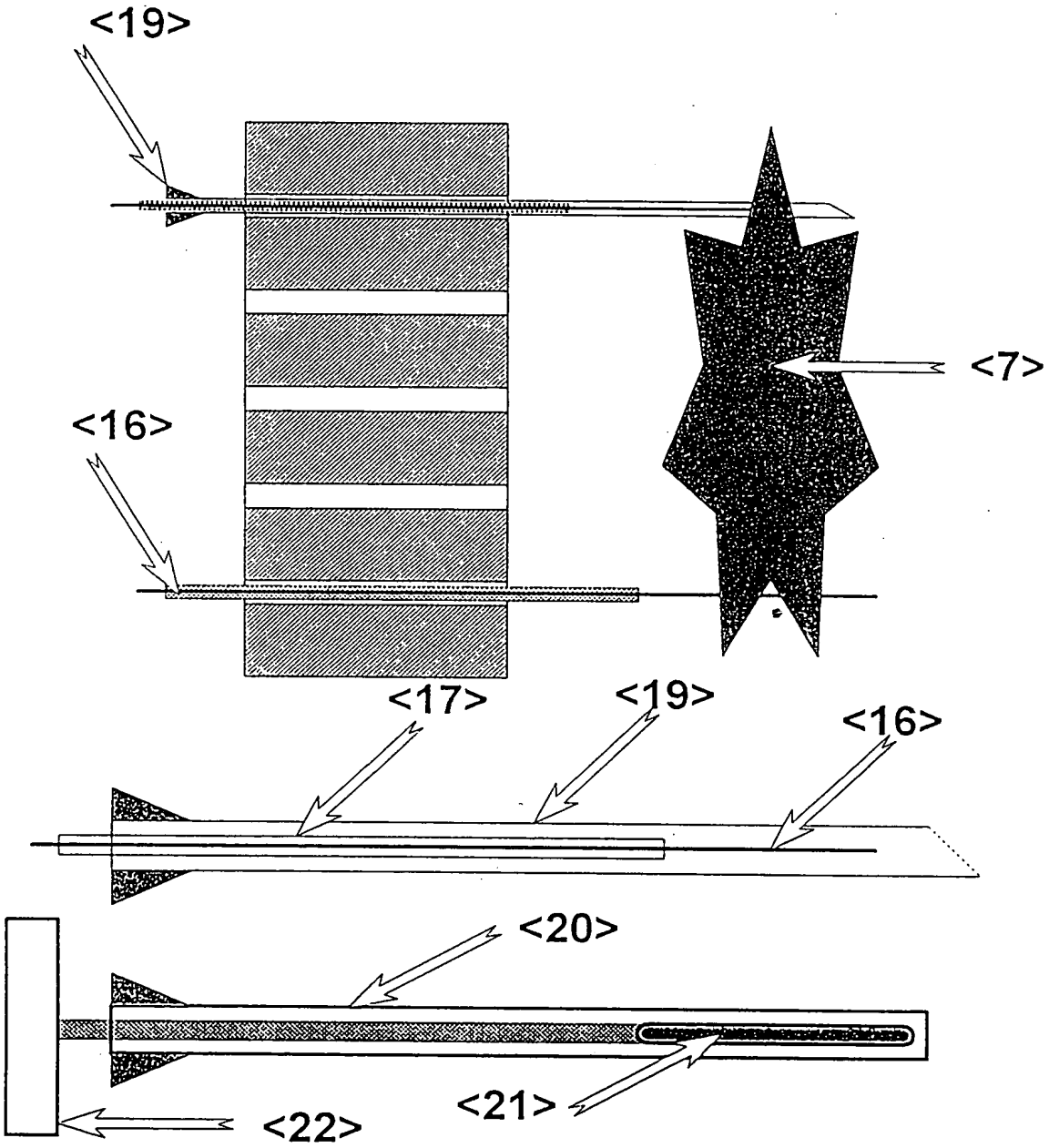


Fig. 6 d



20 -05- 1999

Fig.7 a-c

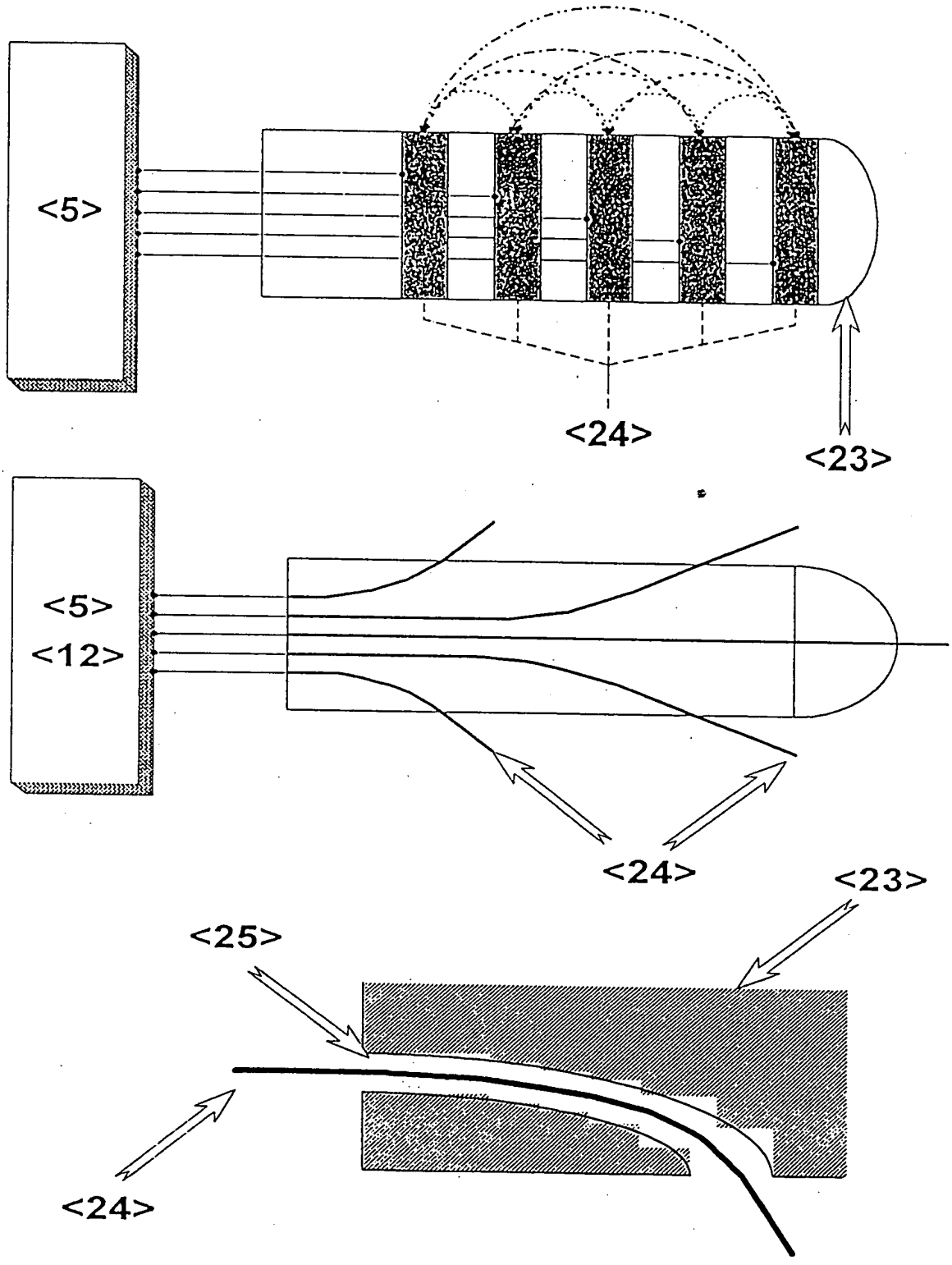


Fig. 8

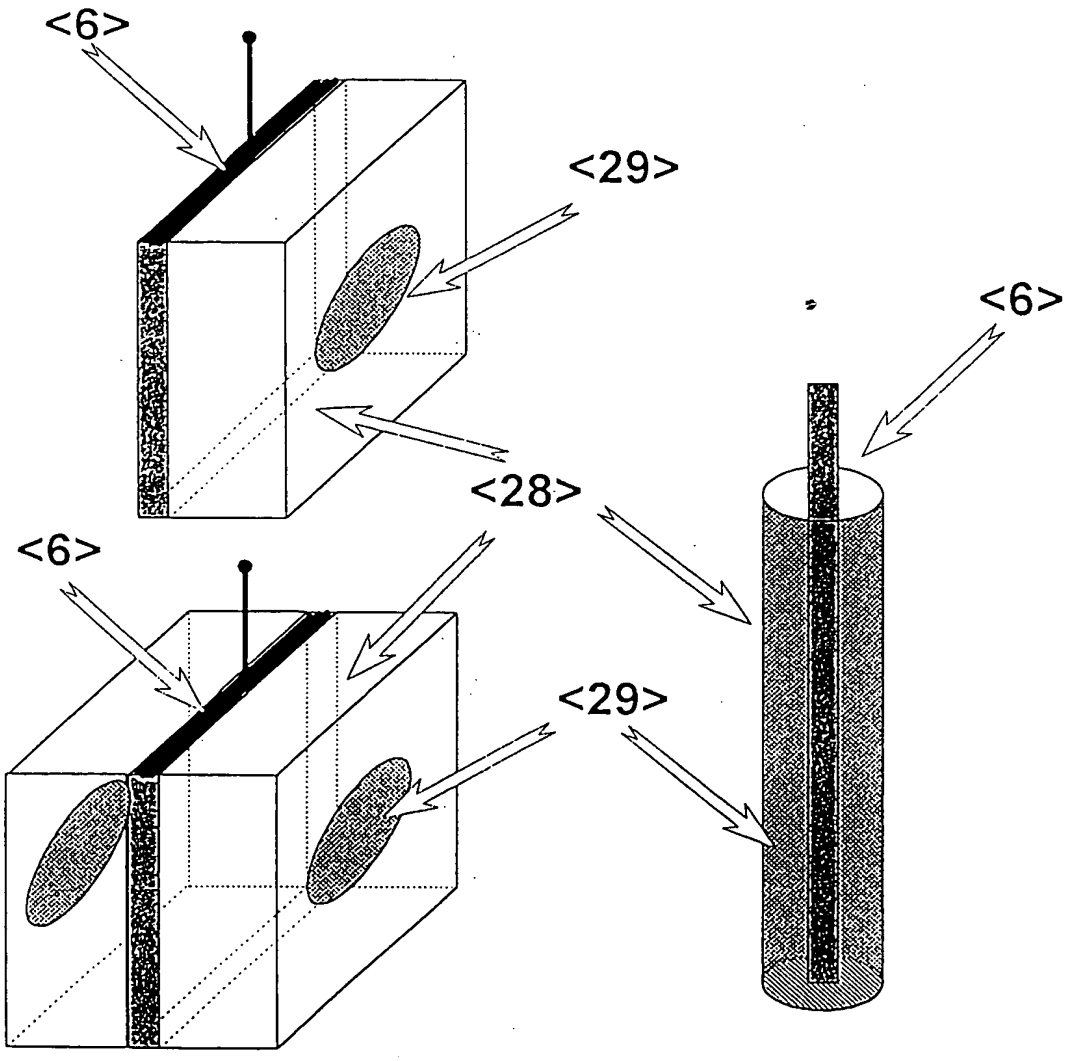


Fig. 9 a-e

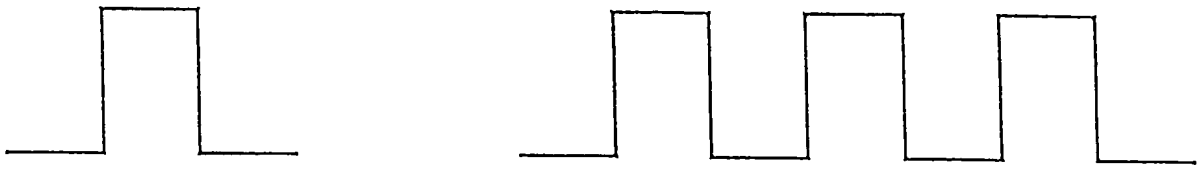


Fig. 9 a

Fig 9 b

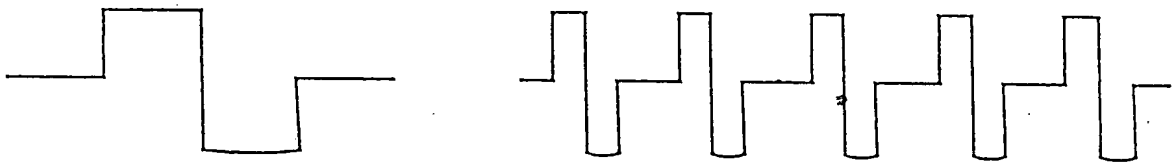


Fig 9 c

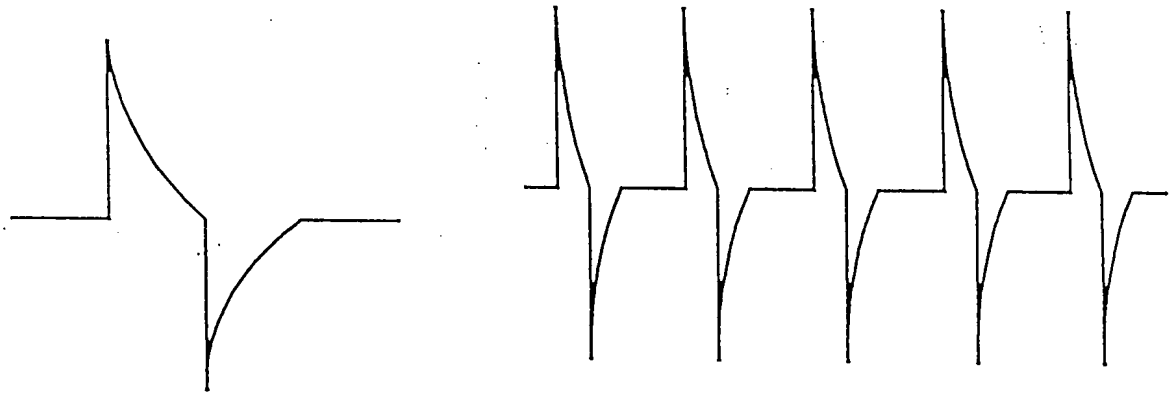


Fig. 9 d

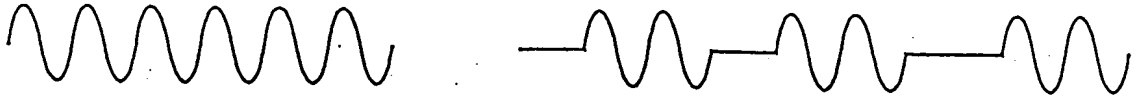


Fig 9 e

Fig. 10

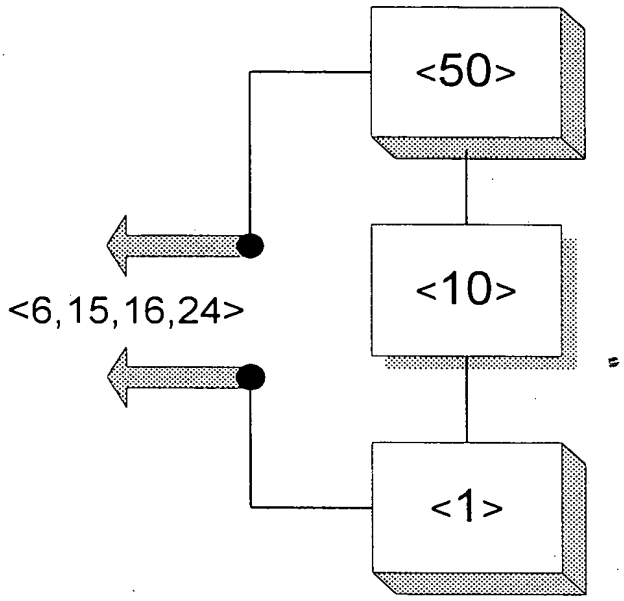
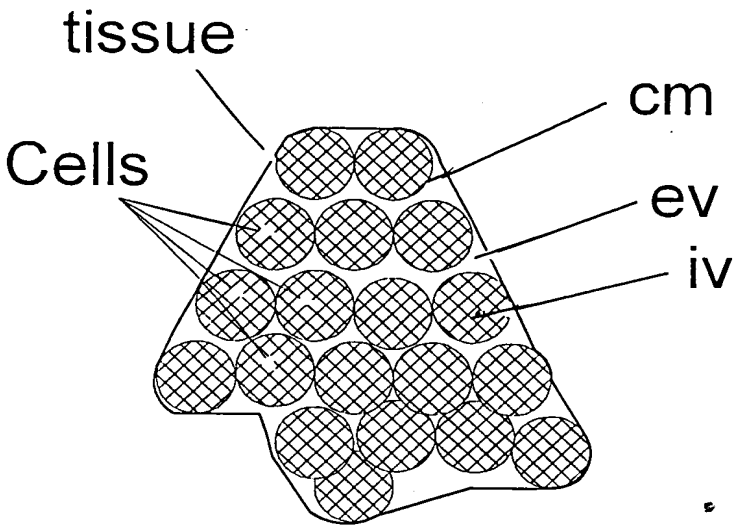


Fig. 11 a,b



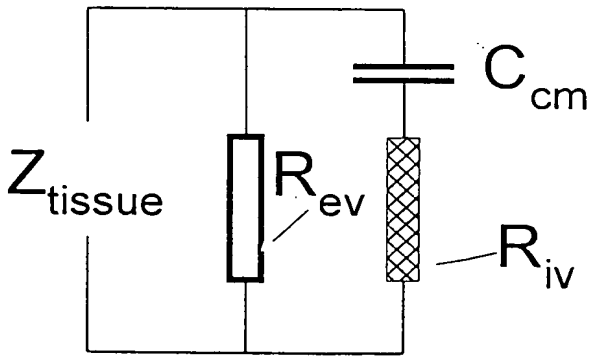
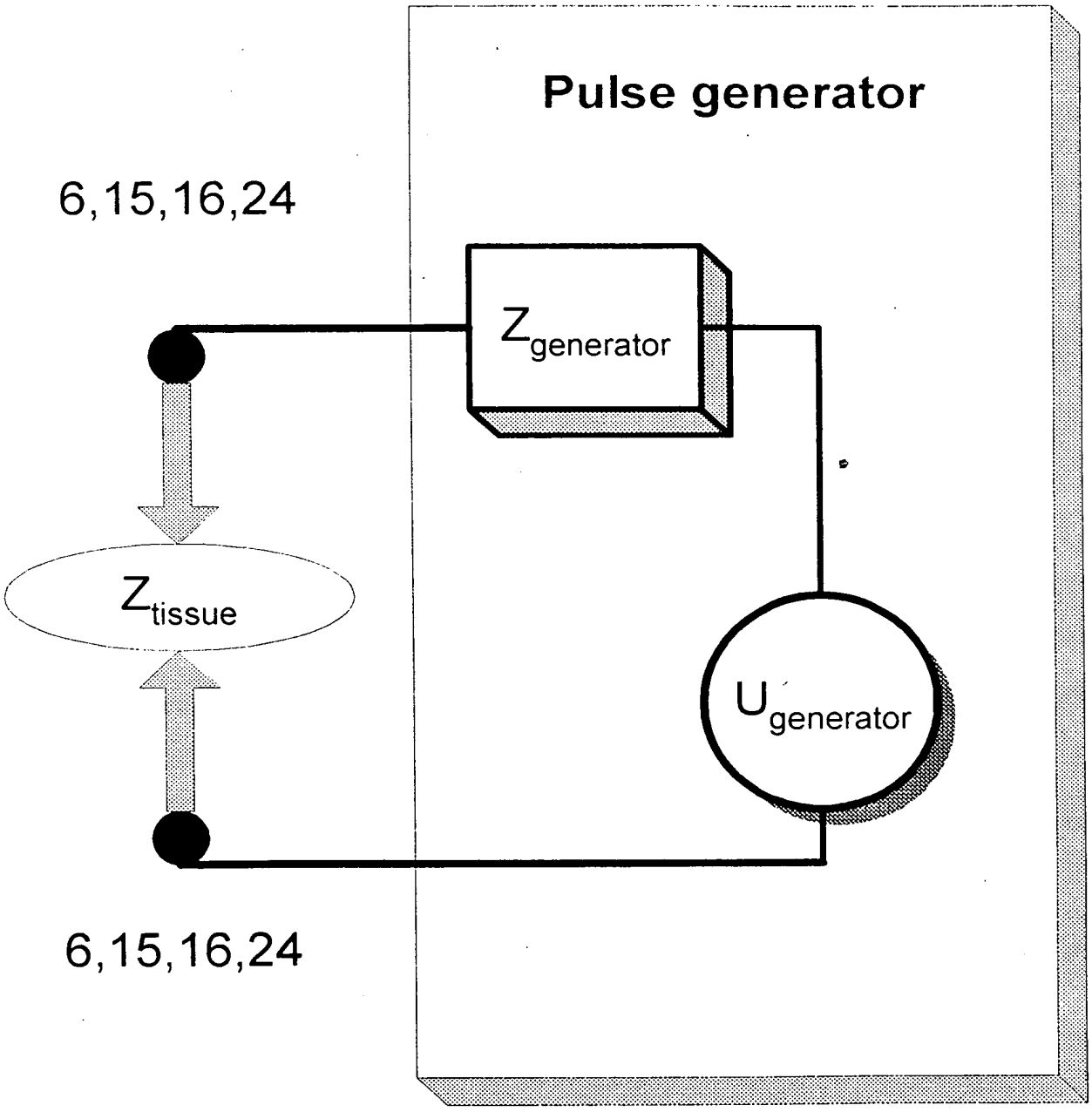


Fig. 12



PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61N 1/30, A61B 5/05

A1

(11) International Publication Number: WO 99/52589

(43) International Publication Date: 21 October 1999 (21.10.99)

(21) International Application Number: PCT/SE99/00511

(22) International Filing Date: 30 March 1999 (30.03.99)

(30) Priority Data:
9801139-8 31 March 1998 (31.03.98) SE

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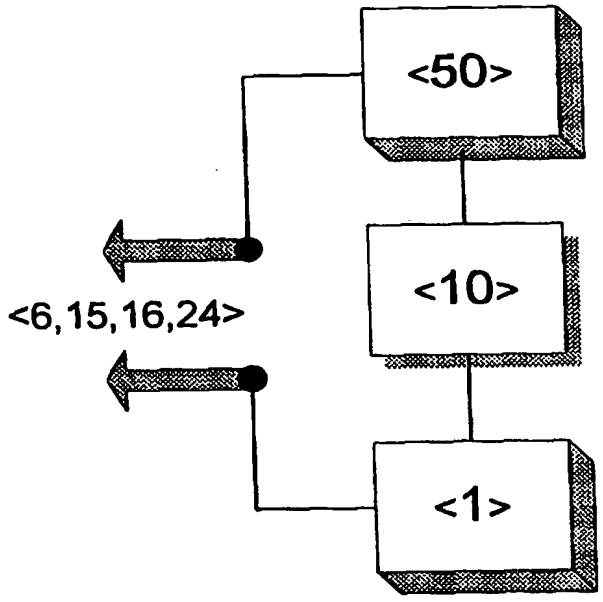
(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.
In English translation (filed in Swedish).

(54) Title: AN APPARATUS FOR CONTROLLING THE GENERATION OF ELECTRIC FIELDS

(57) Abstract

An apparatus (60) according to the present invention includes a voltage generator (1) for generating brief voltage pulses for the impression of voltage on electrodes (6, 15, 16, 24) included in the apparatus, and a measurement unit (50) which is coupled to the electrodes. These are designed to be secured at or inserted in tissue in a restricted region of a human or an animal in order therebetween to form electric fields in the tissue. The measurement unit (50) is disposed to determine the impedance between the electrodes which is substantially determined by the electric properties of the tissue which is located between the electrodes. A registration and calculator device (10) forms a control unit which, based on the impedance determined by the measurement unit, controls the output voltage of the voltage generator such that the electric field which is formed in the tissue always has a predetermined value. The treatment with the electric field realizes a perforation of cell membranes in the tissue which thereby permits the passage of substances fed to the body (e.g. cytostatic or genetic material).



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AN APPARATUS FOR CONTROLLING THE GENERATION OF ELECTRIC FIELDS

The present invention relates to an apparatus for generating pulses of electric fields in a restricted area of a human or an animal according to the preamble to the appended independent Claim.

The therapy forms which are routinely employed in modern medical care for tumor therapy are examples of treatment types where the outcome of such treatment is unsatisfactory. For example, in tumor therapy unsuccessful attempts are often made to achieve local tumor control, which is the cause of mortality of approximately 30% of cancer patients. It is, therefore, important to develop a new and improved technique for local and regional tumor treatment.

In today's medical care, surgery, chemotherapy and radiation therapy, also known as radiation treatment, or combinations hereof are the most commonly employed methods for treating malignant tumors. Approximately every second patient suffering from infiltrating cancer is treated with radiation therapy, but only roughly half of the patients are cured. This failure is, on the one hand, the cause of the presence of widespread disease (distal metastasis) or relapses (the return of tumors in the treated area), and on the other hand because certain types of tumor are resistant to radiation treatment or chemotherapy.

With varying success, attempts have been made to reinforce and improve the efficiency of radiation therapy in sterilizing tumors. For example, use has been made of more sophisticated radiation therapy techniques, such as stereotactic treatment, "conformal radiotherapy", of altered fractioning or added pharmaceuticals to increase the radiation sensitivity of the tumors.

Use is also made of heat as an adjuvant ionizing radiation, which, for certain tumor forms, may increase the number of complete remissions by up to a factor of two.

Also in certain purely medically treated diseases in local organs, the outcome of treatment is occasionally insufficient. It is obvious that, in addition to the wishes which exist regarding improved techniques for treating, for example, tumors, there are not only wishes but also needs for a more efficient technique for treating certain other diseases. In, for example, the local treatment of local organs or tumors, it is a major advantage if, on each treatment occasion, it is possible to adapt the intensity of the treatment to suit the status of the tissue in the local region or in the organ being treated.

According to the present invention, use is made of a series of brief high voltage pulses for generating electric fields in the local region or in the organ which is to be treated. In the continuation of this description, use will also be made of the expression High Voltage Impulse Therapy, occasionally abbreviated to HVIT.

The treatment with electric fields realizes a perforation of the cell membranes which thereby allow the passage of substances (e.g. cytostatic or genetic material) added to the body. The treatment involves increased inflow of therapeutic substances, whereby the effects of chemotherapy are amplified. The outflow of specific substances out of, for example, tumor cells moreover often realizes a stimulation of the immune system. In total dielectric collapse, the result is often achieved that the cells are sterilized directly by the electric fields formed by the high voltage pulses. In clinical experiments, the method has proved to be effective in combination with cytostatics (Bleomycin) for, for example, treating melanoma and tumors in the neck, head, liver, pancreas and lungs.

In HVIT, the treatment result is determined by the number and duration of the high voltage pulses to which the tissue is subjected and how high electric field forces the impressed pulses create in the tissue, as well as the form or frequency the pulses possess. In order to achieve an effective and dependable treatment, it must be possible to control all of these physical parameters. Biological properties which affect the treatment result are, among other things, the electric conductive capacity of the tissue, its dielectric properties, the cell

sizes and the structures of the cell membranes. All of these properties vary between different tissues. In order to achieve optimum treatment effect, it is therefore necessary to measure how the electric properties of the tissue change between each high voltage pulse or between the series of pulses, i.e. to establish when the cells are sufficiently perforated.

In previously employed HVIT, it was not possible to monitor when the tissue was sufficiently perforated, i.e. when the treatment was completed, which entailed that the tissue was occasionally undertreated and occasionally overtreated. This involved a degree of uncertainty in the treatment result. A typical HVIT treatment according to prior art techniques entails that an applicator was placed over the tissue which was intended for treatment. The high voltage generator was, for example, set such that the outgoing voltage corresponded to a field force in the target volume of approx. 1300 V/cm. The treatment was completed with a fixed number of pulses which it was known normally gave the desired result. The weaknesses in this procedure were, on the one hand, that the size of the electric field which the generator in reality generated in the tissue of the target volume was unknown, and, on the other hand, that it was not possible to assess when the treatment was sufficient.

The present invention relates to an apparatus which includes mechanical devices for subjecting a tissue within a restricted region or an organ in a person or an animal for one or more pulses of an electric field at a field strength, configuration, duration and frequency adjustable for the relevant treatment occasion. The expression "duration" relates to both the length of the pulses and the number of pulses, the expression "frequency" relates to both how often the pulses are repeated and the frequency with which the field alternates during an ongoing pulse.

The characterizing clause of the appended independent Claim discloses a technique which entails a substantial improvement to the efficiency of surgery, chemotherapy and radiation therapy. The technique is also applicable within modern molecular medicine where substances and

genetic DNA sequences which are to be introduced into tissue cells are customized.

Further expedient embodiments of the present invention are disclosed in the appended subclaims.

The present invention will now be described in greater detail hereinbelow, with reference to a number of Figures, in which:

Fig. 1 is a block diagram of a fundamental apparatus for applying electric fields in a restricted region of a person or an animal;

Fig. 2 is a block diagram of a fundamental apparatus for applying electric fields and/or ionizing radiation in a restricted region of a human or an animal;

Fig. 3 is a block diagram of one embodiment of a combination of devices for forming electric fields in a restricted region of a human or an animal;

Figs. 4a-d are embodiments of electrode applicators for external treatment of tissue;

Fig. 5 shows one embodiment of an electrode applicator for intraoperative treatment of, for example, tumors and superficial tumor nodules;

Figs. 6a-d show embodiments of electrodes and electrode applicators designed for interstitial treatment of tissue;

Figs. 7a-c show embodiments of electrodes and electrode applicators designed for the treatment of, for example, tumors in bodily cavities and in organs accessible via large vessels;

Fig. 8 shows embodiments of electrodes in which these are disposed for combination treatment with antitumoral pharmaceutics;

Figs. 9a-e show examples of configurations of voltage pulses applied to the electrodes;

Fig. 10 is a simplified block diagram of one embodiment of the apparatus;

Fig. 11a shows a model of the principle structure of living tissue;

Fig. 11b is an electric skeleton diagram of the electric structure of living tissue; and

Fig. 12 is an electric model of a pulse generator connected to living tissue.

Fig. 1 shows, in block diagram, the basic design of a high voltage generator 1, electrodes 6,15,16,24 and a registration and conversion device 10, for example a computer or a microprocessor 10, these devices all being included in the apparatus according to the present invention. Hereafter, the word computer will also be employed without any restrictive intent for the registration and conversion device. Between the high voltage generator 1 and the electrodes 6,15,16,24, there are disposed one or more signal connections 32 and electric conductors 33. Between the computer 10 and the high voltage generator 1, and between the computer and the electrodes 6,15,16,24, there is provided one or more signal connections 32. While the signal connections 32 in the Figure are shown as directly connecting the computer and the electrodes, it will be obvious that the apparatus as such also includes devices described in the continued description of this application, such as switches 3, distributor 4, electrode applicator 5, etc. for controlling the voltage impressment of the electrodes, etc.

Fig. 2 shows one embodiment of the present invention in which a radiation transmitter 34 is connected via signal connections 32 to the

computer. In certain embodiments, the radiation transmitter is mechanically interconnected to the high voltage generator, while in other embodiments it only has signal connection with the combination of devices illustrated in Fig. 1.

Fig. 3 schematically shows one embodiment of a combination of devices for generating electric fields according to the present invention. The Figure shows blocks for a high voltage generator 1, a capacitor battery 2, a switch 3, a distributor 4 for distributing the high voltage pulses which are generated on discharge of the capacitor battery 2 through the switch 3 to an electrode applicator 5 and electrodes 6 intended to be placed in or adjacent the tissue region 7 or organ 7 of a patient undergoing treatment. The high voltage generator 1, the capacitor battery 2, the switch 3 and the distributor 4 are connected in series with one another by means of electric conductors 33. Between the distributor 4 and the electrode applicator 5, there is provided at least one electric conductor 33 and at least one signal connection 32. Via the signal connections 32, the distributor 4 controls the voltage impression of the electrodes of the electrode applicator, via which the electric conductors 33 are interconnected to the distributor 4 and via the electric conductor 33 to the switch 3. In one alternative embodiment, each electrode 6 is electrically connected to the switch 3 by means of an electric conductor 33.

As a rule, the distributor 4 or an electrode applicator impresses voltage simultaneously on only two electrodes 6, while the other electrodes are permitted to assume that potential which is determined by the placing of the electrode in the treatment region. The term voltage impression also includes in this context the fact that one or more electrodes are earthed (have zero potential). The switch 4 and/or the electrode applicator 5 are disposed to permit, if so wished, the voltage impression pairwise of all electrodes which are placed in the treatment region. It will be obvious to a person skilled in the art, that, in certain embodiments, the devices are provided in order, on voltage impression, to allocate to several electrodes a substantially corresponding (the same) potential.

All units are, via signal connections 32 which, in certain embodiments, are wholly or partly wireless, connected to a registration and conversion device 10 with a screen 10a. Hereafter, the designations control and conversion unit 10 or computer 10 will be employed for the registration and conversion device. The computer 10 constitutes a control and monitoring device for the function of the apparatus.

The expression electrode applicator 5 relates to a retainer member for the electrodes 6, where the retainer member is designed to facilitate the correct application of the electrodes at or in the treatment region.

The computer is set as a rule for the high voltage pulses to contain the following data:

repetition frequency	approx. 0.1-10000 per second
amplitude	approx. 50-6000V
pulse length	approx. 0.1-200 ms
number of pulses	1-2000 per treatment.

The pulses are applied before, during or immediately after the radiation treatment. Examples of pulse configuration employed are square pulse with a pulse length of 0.1-2 ms or exponentially fading pulse with a time constant RC approximately equal to 0.1-2 ms. In large amplitudes of the voltage, shorter pulse lengths are generally selected, and vice versa.

The high voltage generator 1 is, as a rule, disposed to emit modulated a.c. voltage of a frequency within a range of 40 Hz-2 MHz and as a rule within the range of 40 Hz-100 kHz. In those embodiments where the high voltage generator is disposed to emit a.c. voltage of high frequency, a modulator is employed instead of a capacitor battery and switch for generating short modulated high frequency pulses with a pulse length within the range of approx. 0.1-200 ms.

As will be apparent from the embodiment illustrated in Fig. 3, the apparatus generally also includes sensors 8 intended to be applied to

the patient in the treatment region. The sensors are connected via a detector interface 9 to the registration and conversion device 10. On application of the treatment pulse, a signal is generated in the sensors 8 which, via the interface 9, is transferred to and registered in the computer 10. From the measured signals, the computer calculates the electric field force induced by the pulse and the electromotive force in different parts of the treatment region 7. These signals entail that the computer 10 emits signals to the high voltage generator/capacitor battery (feedback) to adjust the amplitude of the generated pulses so that the predetermined field force is achieved in the treatment region. This monitoring and adjustment take place continuously during the application of the pulses.

Figs. 4a-d show embodiments of electrode applicators 5 for external treatment of a patient with the electrodes 6 applied in a restricted region on the patient and in different configurations around the tissue region 7, for example a tumor 7, which is to be treated. Figs. 4a and 4b show how by crosswise application of the electric high voltage pulses to different combinations of two electrodes 6, the result will be achieved, as marked in the Figure by the electric field force lines, that the electric field passes through all parts of the tissue region 7.

Figs. 4c-d show how electrodes are designed with abutment surfaces of different sizes in order for the field lines to be focused to the desired treatment region. At the beginning of the treatment, the electric high voltage pulses have, for example, a voltage which is adjusted in accordance with the distance between the electrodes. The voltage is then adjusted in accordance with the relationship:

Voltage = (constant) x (the distance between the pairwise electrodes). The value of the constant is varied in response to the type of tissue and is, as a rule, selected at values between approx. 500-3000 V/cm.

Once the treatment has commenced, the control unit and impedance measurement unit described below regulate the output voltage of the

pulse regulator to values which entail that the sought-for electric field force passes through the tissue.

Fig. 5 shows one embodiment of an electrode applicator 5 for intra-operative treatment, and treatment of, for example, superficial tumor nodules 7. The electrode applicator has a scissors-like design and comprises two shanks 12 of electrically insulating material (e.g. teflon) which are movably interconnected to one another in a journal 11. The shanks are provided with a gripping lock 13. At one end of each shank 12, the shanks are provided with finger grips and at the other ends with electrodes 6 which grasp about the tumor nodules 7. The grip locks 13 fix the shanks 12 in the set position. The voltage of the electric high voltage pulses is adjusted in response to the size of the tumor 7 with the aid of a distance sensor 14 built into the electrode applicator and connected to the computer 10. The voltage is set at the beginning of the treatment, for example according to the relationship:

Voltage = (constant) x (the distance between the pairwise electrodes). The value of the constant is adapted to the type of tumor and is, as a rule, selected within the range of approx. 500-3000 V/cm.

Once the treatment has commenced, the control unit and the impedance measurement unit described below regulate the output voltage of the pulse generator to values which entail that the sought-for electric field force passes through the tissue.

Figs. 6a-d show embodiments of electrodes 15,16 and a fixture 18 for the electrodes, where the electrodes and the fixture are suitable for use for interstitial treatment of both superficial and profound tissue. Fig. 6a shows the electrodes 15,16 in two different embodiments, namely in one embodiment in which the electrodes 15 are needle-shaped and in one embodiment in which the electrodes 16 are stiletto-shaped. Each one of the electrodes 15,16 is, in a portion 31 most proximal their one end, provided with an electric conductor 33 for connection to the high voltage generator 1. The above-mentioned portion is provided with an electrically insulating layer 17 or an electrically insulating sleeve 17 in which the electrode is inserted.

The electrodes are applied in different configurations in and about the tissue 7 or the organ 7 which is to be treated, either direct by free hand or with the aid of an electrode applicator (fixture) 18 provided with a hole. The electrode applicator is, as a rule, designed so as to be removed from the electrodes 15,16 once these have been applied on the patient. It will thereby be possible to allow the electrodes to remain in position in the patient to be used on several subsequent treatment occasions. Alternatively, the electrode applicator is removed together with the electrodes 15,16 after each treatment. Also in interstitial treatment, there are electrodes with surfaces of different sizes for controlling the extent of the electric fields.

Those parts of the electrodes 15,16 which are intended to be inserted into the patient to cover the extent of the tissue 7 which is to be treated are, for example, manufactured of stainless steel of a quality which agrees with or corresponds to that employed for injection syringes or are manufactured or coated with another tissue-friendly metal such as a noble metal, for example gold or platinum. The remaining portion of the electrodes forms an insulated portion 17 with input conductors 33 for the high voltage pulses. On the employment of flexible input conductors, the electrode is placed in a large cannula 19 which, after application of the electrode in the patient, is withdrawn, the electrodes remaining in position in the tissue.

In certain embodiments, the electrodes consist of radioactive metal (e.g. iridium-192, cobalt-60) or are surface coated with radioactive substances (e.g. iodine-125). In other embodiments, they are designed as tubes 20 of inert metal which are charged with radioactive material (e.g. ^{192}Ir, ^{137}Cs, ^{226}Ra) which advantageously takes place by the employment of a so-called after loading device 22. The pulses have a voltage which, at the start of the treatment, for example are determined by the distance between the electrodes. The voltage is then set according to the relationship:

Voltage = (constant) x (the distance between pairwise electrodes).

The value of the constant is selected in response to the type of

tumor and, as a rule, selected within the range of approx. 500-3000 V/cm.

Once the treatment has commenced, the control unit and the impedance measurement unit described below regulate the output voltage of the pulse generator to values which entail that the sought-for electric field force passes through the tissue.

In those applications where treatment with electric fields is combined with radiation treatment from a radiation source which is located outside the treatment region, the electrodes in the treatment region are supplied with electric voltage pulses before, during or immediately after the radiation treatment.

Figs. 7a-c show electrodes 24 for treating tissue accessible via, for example, major vessels, or via bodily cavities, for example respiratory tracts, urinary tracts and stomach-intestinal trait. The electrodes are disposed on the surface of a cylinder-like electrode applicator 23 of insulating material 17. In certain embodiments, the electrodes are designed such that they are introduced into the tissue through channels 25 in the applicator 23 operated by a remote control. As will be apparent from Fig. 7c, the channels 25 (according to the embodiment described in the preceding sentence) discharge in the circumferential surface of the electrode applicator, whereby the electrodes 24 are, on their displacement, guided into tissue surrounding the electrode applicator. In certain embodiments, the applicator is disposed to be supplied with radioactive preparations, whereby the applicator also forms a radiation device. The applicator is disposed to be supplied with the radioactive preparations manually or by means of an after loading device 22. The voltage of the electric high voltage pulses is adjusted during the treatment.

The field lines in Fig. 7a indicate the extent of the electric field lines in the tissue.

For intracavity treatment of tissue in different, irregularly shaped bodily cavities (e.g. oral cavity, respiratory tracts, oesophagus, stomach, uterus, bladder, ureter, rectum) electrode applicators 23 are

applied as is apparent from Figs. 7a-c, particularly designed in response to the configuration of the cavity, with electrodes applied on the surface 24 or alternatively designed as needles which, through channels 25, are passed into the tissue by remote control. These applicators are suitable for use when treating, for example, lung cancer, liver tumors, renal tumors and tumors in the stomach-intestines with reduced absorbed dose for reducing side effects of the radiation treatment in normal tissue. Prostate cancer is treated with applicators applied via the rectum and the ureter. These applicators are, in certain embodiments, designed to be charged with radioactive sources or radioactive material 21, either manually or using an after loading device 22.

Fig. 8 shows an apparatus for combined treatment with antitumoral pharmaceutics where the electrode 6 is coated with a layer 28 of porous metal, glass, ceramics, inert plastic or other polymer which contains antitumoral pharmaceuticals 29 (e.g. bleomycin, platinol, taxol, monoclonal antibodies), genetic material (chromosomes, DNA) or radioactive substances (e.g. iodine 125, Auger-electron emitters) 29. This type of electrode is well suited for use in radiation therapy, since the high electric field force increases the permeability of the tumor cell for the above mentioned substances and thereby increases the antitumoral effect.

Figs. 9a-e show examples of pulse forms in the voltage pulses which are pairwise applied to the electrodes 6,15,16,24. In the Figures the height of the pulse represents the voltage between two electrodes. The width of the pulse represents the length of the pulse. The Figures 9a and 9c show examples of square pulses, Figs. 9b and 9d examples of pulses whose voltage fades with time, and Fig. 9e pulses of alternating voltage. Figs. 9c and 9d show voltage pulses where, analogous to that which applies in alternating voltage, the electrodes alternatingly have the highest voltage, whereby a corresponding change takes place of the electric field between the electrodes.

The above described electrodes 6,15,16,24, the voltage generator 1, the control and converter device 10, also previously designated the

computer and an impedance measurement unit 50 are included in the block diagram shown in Fig. 10. The voltage generator, the computer, the electrodes and the impedance measurement unit are interconnected with one another by electric conductors for impressing voltage on the electrodes and for transferring signals. It will be obvious to a person skilled in the art that, in certain embodiments, at least a part of the signal connections are designed as wireless connections.

Fig. 11a shows the basic structure of living tissue, while Figure 11b shows an electric outline diagram for the electric structure of the tissue. The correspondences between the resistances and the capacitance in the electric diagram and in the tissue are apparent from the designations of the components and the continued description.

Fig. 12 shows the basic electric structure of a pulse generator 1, previously also designated high voltage generator. The Figure shows how the impedance of the tissue Z_{tissue} via the electrodes 6,15,16,24 is connected in series to the inner impedance of the pulse generator $Z_{generator}$. Reference letter U relates to electromotive force (EMF) of the pulse generator.

It will be obvious to a person skilled in the art that the above described mechanical units, in certain embodiments of the present invention, form mutually separate mechanical units which are interconnected with each other by means of electric conductors and signal connections, while, in other embodiments, some or all of these units, with the exception of the electrode applicator and the electrodes, form a mechanical unit which is co-ordinated with the voltage generator, the impedance measurement unit or the computer.

As will have been apparent from the foregoing description, the present invention relates to an apparatus for high voltage impulse therapy (HVIT) with detection of the treatment effect. The apparatus includes an impedance measurement unit which, on treatment of tissue or organs, is employed for measuring the electrical impedance of the tissue. The impedance measurement unit is, as a rule, disposed to measure the impedance of the tissue at, at least, one frequency. Normally, the

impedance measurement unit is disposed to measure the impedance of the tissue within a frequency range, e.g. within the range of 10 Hz to 10 Mhz. With the aid of a mathematical algorithm, a test magnitude is calculated whose value is a measurement of the treatment effect.

The voltage across the tissue will be in accordance with that shown in Fig. 12:

$$U_{tissue} = U_{generator} * Z_{tissue} / (Z_{tissue} + Z_{generator})$$

The impedance of the tissue varies extremely, depending upon the cell structure and build up of the tissue, the nature of the surrounding tissue and the quantity of bodily liquids which are found in and around the treated region. Since the output impedance of the generator is not slight in relation to the impedance of the tissue, the output voltage will vary greatly depending upon where and how the applicator is placed. It has proved, in practical experiments, that even if an applicator is placed at the same point, marked with a colour on the body, the impedance will vary greatly from time to time, depending upon minor differences in placing and contact impedance, as well as differences in fluid quantity and the nature of the tissue.

In order to be able to predict the actual pulse voltage from the pulse generator, the impedance of the tissue must be known at any time. Only if the output voltage from the generator is adjusted on the basis of the generator's output impedance and the impedance of the relevant tissue will it be possible to achieve a predictable and constant effect. According to the present invention, the apparatus includes means for measuring the impedance of the treated tissue and means for employing this information for controlling the output voltage of the pulse generator such that the desired field force is always achieved in the tissue.

Fig. 10 illustrates such a system. A control unit is included in the apparatus and measures, with the aid of the impedance measurement unit, the impedance of the tissue. The control unit adjusts the output voltage from the generator so that the desired field force is achieved.

In the control unit, which, for example, is a PC, the desired field force is set whereafter the control unit measures the impedance in the tissue and calculates the requisite pulse voltage from the generator. When a pulse is subsequently applied, the field force will always be constant, since the control unit always measures and adjusts the voltage from the generator before the pulse is generated.

With the system in Fig. 10 the sought-for effect will be achieved, e.g. to maintain a constant output voltage from the pulse generator independently of the impedance in the tissue. It also proves that a system according to Fig. 10 is excellent for measuring and assessing the treatment result achieved in HVIT. By measuring impedance and carrying out analysis of impedance change in the tissue after a pulse has been applied, the documentary support is given for assessing when the treatment is completed and no more pulses are needed or give a further positive effect. This method builds on the tissue model shown in Fig. 11a,b.

The impedance in tissue substantially consists of three components, the resistance in the extra cellular fluid, the resistance in the intra cellular fluid and the capacitance which is formed between the D.C. insulating effect of the cell membrane. In the model, we have combined the impedance effect of the cell core with the resistance in the intracellular fluid. At low frequencies, only current will flow through the extra cellular liquid and the impedance is determined substantially by R_{ev}. At medium-high frequencies, the capacitance of the cell membrane C_{cm} together with the resistance of the intracellular liquid, R_{iv}, will begin to effect the impedance. At high frequencies, substantially the components R_{ev} and R_{iv} will effect the impedance of the tissue. Thus, the result will be a frequency dependence in the impedance of the tissue which is largely dependent on the thickness of the cell membrane and the formation of the cells. At low frequencies, the impedance is approximately R_{ev} and at high frequencies $R_{ev}//R_{iv}$. The symbol // is employed to indicate that R_{ev} is connected in parallel with R_{iv}.

$$Z_{tissue} = R_{ev} // (R_{iv} + C_{cm})$$

Since the treatment with electric fields is intended to render the cell membrane permeable or to wholly destroy it, a clear indication will be obtained by measuring the change in C_{cm} as to whether the treatment is completed or not. When all cell membranes in the tissue are destroyed, no change of C_{cm} will take place any longer and the tissue is ready-treated.

Table 1 below illustrates a compilation of impedance measurements taken during the treatment of rats with tumors.

Table 1 Measured tissue impedance in ohm in rats with tumor

Frequency/Pulses	0 pulses	16 pulses	32 pulses	48 pulses	64 pulses
10 Hz	232.24	160.12	160.36	172.53	179.3
15 Hz	229.42	157.76	151.48	163.37	159.61
20 Hz	200.28	145.46	138.84	148.89	141.78
30 Hz	173.9	134.11	127.56	132.16	125.87
50 Hz	153.7	122.75	116.44	120	112.29
70 Hz	144.46	116.39	110.38	136.26	105.58
100 Hz	137.64	110.69	105.13	105.47	100.31
150 Hz	130.68	104.86	99.79	99.71	95.35
200 Hz	125.81	100.97	96.31	96.23	92.26
300 Hz	120.3	96.27	92.06	92.19	88.73
500 Hz	113.96	91.09	87.49	87.84	84.91
700 Hz	109.83	87.88	84.68	85.16	82.6
1000 Hz	105.88	85.03	82.2	83.03	80.62
1500 Hz	101.99	82.12	79.71	81.84	78.59
2000 Hz	99.34	80.27	78.02	79.54	77.69
3000 Hz	96.12	77.98	76.06	77.18	75.72
5000 Hz	92.28	75.4	73.81	74.85	73.71
7000 Hz	89.72	73.85	72.41	73.86	72.54
10000 Hz	87.38	72.45	71.14	73.52	71.43
15000 Hz	84.91	70.91	69.71	72.53	70.15
20000 Hz	83.18	69.75	68.62	71.51	69.17
30000 Hz	80.8	68.23	67.14	69.81	67.8
50000 Hz	77.73	66.26	65.28	68.24	65.97
70000 Hz	75.62	64.79	63.9	66.67	64.65
100000 Hz	73.01	63.01	62.11	64.62	62.93
150000 Hz	70.42	61.05	60.3	64.06	61.19
200000 Hz	68.3	59.37	58.76	61.93	59.65

It will be apparent from Table 1 that the impedance reduces at low and medium-high frequencies after treatment with pulses. The reduction principally takes place after the introductory 16 pulses and the change rapidly fades thereafter. Thus, the rat is substantially ready-treated already after the first 16 pulses and further treatment after 32 or 48 pulses gives no major change in C_{cm}. The measurement data in Table 1 indicates that the treatment is completed after 32 pulses. In order to confirm this assessment, the measured measurement values have been taken and treated as described below.

Table 2 shows the impedance change in per cent at different frequencies after the electric fields generated by 16 voltage pulses have passed through the tissue. In the Table, the change of the impedance is given in per cent which occurred each time when a series of electric fields generated by the voltage pulses has passed through the tissue.

Table 2 Impedance change in per cent after treatment with 16 pulses at a time

Frequency/Pulses	16 pulses	32 pulses	48 pulses	64 pulses
10 Hz	-31.05408	0.1033414	5.2402687	2.9150878
15 Hz	-31.23529	-2.737338	5.1826345	-1.638916
20 Hz	-27.37168	-3.305372	5.0179748	-3.55003
30 Hz	-22.88097	-3.766532	2.6451984	-3.617021
50 Hz	-20.13663	-4.1054	2.3162004	-5.016265
70 Hz	-19.43098	-4.160321	17.914994	-21.23771
100 Hz	-19.58006	-4.039523	0.2470212	-3.74891
150 Hz	-19.75819	-3.879706	-0.061218	-3.336394
200 Hz	-19.74406	-3.703998	-0.063588	-3.155552
300 Hz	-19.97506	-3.499584	0.1080632	-2.876143
500 Hz	-20.06845	-3.159003	0.3071253	-2.571078
700 Hz	-19.98543	-2.913594	0.4370391	-2.330875
1000 Hz	-19.6921	-2.672837	0.7839063	-2.276162
1500 Hz	-19.4823	-2.362977	2.08844	-3.186587
2000 Hz	-19.1967	-2.264949	1.5300987	-1.862291
3000 Hz	-18.87224	-1.997503	1.1652102	-1.518935
5000 Hz	-18.29215	-1.723017	1.1270048	-1.235371
7000 Hz	-17.68836	-1.604993	1.6161391	-1.471244
10000 Hz	-17.08629	-1.499199	2.7237354	-2.391852
15000 Hz	-16.48805	-1.413261	3.3211636	-2.802968
20000 Hz	-16.14571	-1.3585	3.4743929	-2.813176
30000 Hz	-15.55693	-1.34901	3.3044554	-2.487624
50000 Hz	-14.75621	-1.260774	3.8080535	-2.920365
70000 Hz	-14.32161	-1.176937	3.6630521	-2.671251
100000 Hz	-13.69675	-1.232708	3.4378852	-2.314751
150000 Hz	-13.30588	-1.065038	5.3393922	-4.075547
200000 Hz	-13.07467	-0.893119	4.6412884	-3.338214

The heading of the Table discloses the accumulated number of pulses of electric fields which have passed through the tissue. On each treatment occasion, a series of 16 pulses is passed through the tissue. That

disclosed in this paragraph for the table heading in Table 2 also applies to the table headings for Tables 3 and 4 used below.

It will be apparent from Table 2, in the same manner as Table 1, that the treatment may be discontinued after 32 pulses, since the impedance change fades dramatically. Table 3 below shows the mean value of the impedance change after different numbers of pulses. The mean value is formed from all measurement frequencies between 10 Hz and 200 kHz. In Table 3, it is clearly seen that the largest impedance change takes place after the first 16 pulses and only a slight change takes place on further treatment.

Table 3 Progressive change in per cent of impedance value at frequencies between 10 Hz-200 kHz

16 pulses	32 pulses	48 pulses	64 pulses
-19.9568	-2.424687	3.1275358	-3.366544

In Table 4, in mean value formation, frequencies below 100 Hz and frequencies over 10 kHz have been deleted. By deleting the lowest frequencies from the mean value, this prevents incorrect impedance values because of disturbance from the motorsystem of the body from influencing the result. The highest frequencies are deleted since the impedance change at these high frequencies is less when C_{cm} is changed and therefore does not contribute to an improved picture of the treatment result.

Table 4 Progressive change in per cent of impedance values at frequencies between 100 Hz-10 kHz

16 pulses	32 pulses	48 pulses	64 pulses
-20.78512	-2.943407	1.0007481	-2.663449

By allowing the control unit in Fig. 10 mathematically to treat and present the measured treatment result as described above, there will be obtained an apparatus which satisfies the wishes of controlling, in the treatment, the strength of the electric field in order to obtain a

basis for discontinuing the treatment at the correct moment and for being able to interpret the direct outcome of the treatment with the electric field.

From the foregoing description, it will be apparent that, in a very simple application of the present invention, the impedance of the tissue is determined at only one frequency. In such instance, a medium-high frequency, e.g. 15 kHz is selected. The inner impedance of the pulse generator is entered in the computer as a fixed value, whereby the impedance of the tissue is determined by a mathematical operation corresponding to that described above. In applications of the present invention, use is however made as a rule of many frequencies in order to eliminate the risks of any possible disruptions which may affect the measurement results.

The system illustrated in Fig. 10 includes means for adjusting the pulse voltage and its frequency content so that the electric field in the treated tissue is always constant regardless of impedance or resistance changes in the tissue. Such means also give a basis for assessing the achieved treatment effect in that it is of a structure which makes it possible to present, for example readily understandable values and graphs which, by mathematical operations, have been extracted from measured impedance or resistance data.

On practical application of the present invention in the embodiment where a radiation transmitter is employed, the radiation transmitter and the electrodes, in certain applications together with the electrode applicator and impedance measurement unit, together form a cohesive mechanical unit. This is of a design which makes it possible, in a restricted region of a human or an animal, to apply both the radiation transmitter and the electrodes in positions where the ionizing radiation is directed at the tissue which is being treated and where the electrodes are in positions in which electric fields between them pass through the tissue. In other embodiments, such means constitute separate parts which, together and where applicable temporarily, or for a lengthy period of time, form a system of devices of a composition corresponding to that described above for the apparatus 40.

The above detailed description has referred to but a limited number of embodiments of the present invention, but a person skilled in the art will readily perceive that the present invention encompasses a large number of embodiments without departing from the scope of the appended claims.

CLAIMS

1. An apparatus (60) for controlling the size of, configuration of and/or duration of electric fields which are generated by a voltage generator (1) between electrodes (6,15,16,24) included in the apparatus or between electrodes (6,15,16,24) connected to the apparatus, where the apparatus includes means (4,5) for distributing the voltage pulses to the electrodes (6,15,16,24) for the formation of the electric fields, and where the electrodes are designed to be secured at a restricted region of a human or an animal or are designed to be inserted in said region, c h a r a c t e r i z e d in that an impedance measurement unit (50) included in the apparatus is disposed, on treatment of tissue or organs adjacent or in said region, to determine the impedance and/or resistance between said electrodes; and that a control and converter unit (10) is included in the apparatus or is connected thereto in order, prior to each voltage pulse or chain of voltage pulses and based on the measurement impedance and/or resistance, to control the size of, number of, configuration of and/or duration of the voltages applied to the electrodes.

2. The apparatus as claimed in Claim 1, c h a r a c t e r i z e d in that the control and converter unit (10) includes a VDU (10a); that the control and converter unit is disposed, prior to the start of the generation by the voltage generator (1) of a pulse or chain of pulses, to show on the VDU (10a) the form of the pulse or chain of pulses calculated by the control and converter unit; and that means are included in said control and converter unit for manual or automatic acceptance of said calculated formation.

3. The apparatus as claimed in Claim 1 or 2, c h a r a c t e r - i z e d in that the electrodes (6,15,16,24) are common for the impedance measurement unit (50) and for said means (4,5) for emitting voltage pulses; or that separate electrodes (4,5) are provided for the impedance measurement unit and said means for emitting voltage pulses.

4. The apparatus as claimed in any of the preceding Claims, c h a r a c t e r i z e d in that the electrodes (6,15,16,24) are disposed, on the treatment, to be placed in a restricted region in a human or in an animal or in positions entailing that the electric fields pass through said region.

5. The apparatus as claimed in any of the preceding Claims, c h a r a c t e r i z e d in that the apparatus includes means (34) for supplying therapeutic substances, genetic material and/or ionizing radiation to said restricted region of a human or of an animal; or that the apparatus is designed to cooperate with such means (34).

6. The apparatus as claimed in any of the preceding Claims, c h a r a c t e r i z e d in that the apparatus includes sensors (8) for detecting electric fields formed by the electrodes (6,15,16,24); and that the sensors are connected to a registration and converter device (10) for calculating the size of the electric field strength in the treatment region; and that, for regulating the amplitude of the voltage pulses applied on the electrodes, the registration and converter device (10) is connected to the high voltage generator (1) and/or to means (2,3,4) connected inbetween the high voltage generator (1) and the electrodes (6,15,16,24).

7. The apparatus as claimed in any of the preceding Claims, c h a r a c t e r i z e d in that the electrodes (6) are disposed to be excited alternatingly and only two at a time.

8. The apparatus as claimed in any of the preceding Claims, c h a r a c t e r i z e d in that the apparatus includes sensors (14) for detecting the distance between the electrodes (6) in each pair of excited electrodes; and that said registration and converter device (10) includes means for adjusting the voltage between the electrodes (6) in each pair of excited electrodes based on the distance between the electrodes.

9. The apparatus as claimed in any of the preceding Claims, c h a r a c t e r i z e d in that the electrodes (6) are designed as needles (15) or stilettos (16).

10. The apparatus as claimed in any of the preceding Claims, c h a r a c t e r i z e d in that the electrodes (6,15,16,24) are wholly surrounded by an electrically insulating layer (17) or have an electrically insulating layer which at least leaves an electrically conductive tip of the electrodes uninsulated.

11. The apparatus as claimed in any of the preceding Claims, c h a r a c t e r i z e d in that an electrode applicator (5,23) is provided for at least temporarily fixing the electrodes prior to the placing of the electrodes on or in the treatment region.

12. The apparatus as claimed in Claim 11, c h a r a c t e r i z e d in that the electrode applicator (23) is of a size and configuration which is adapted to the vessel, bodily aperture or bodily cavity where it is to be placed.

13. The apparatus as claimed in Claim 11, c h a r a c t e r i z e d in that the electrode applicator (5) includes a fixture (18) for fixing the electrodes (15,16) in a fixed pattern.

14. The apparatus as claimed in Claim 11, c h a r a c t e r i z e d in that the fixture (18) is provided with a number of holes for placing electrodes in a desired pattern on each treatment occasion.

15. The apparatus as claimed in Claim 11, c h a r a c t e r i z e d in that the electrode applicator (23) is provided with electrodes (24) placed on the applicator's surface; or that the electrodes (24) are placed in channels (25) discharging in apertures in the surface of the applicator and, by means of remote control, displaceable in the channels and at least partly out through the apertures in order to be inserted into the tissue around the applicator.

16. The apparatus as claimed in any of Claims 1-10, c h a r a c t e r i z e d in that the apparatus includes at least one cannula (19) each one disposed for temporarily enclosing an electrode.

17. The apparatus as claimed in any of the preceding Claims, c h a r a c t e r i z e d in that the electrodes (6,15,16,24) consist of radioactive material or are designed with apertures for accommodating radioactive preparations (21).

18. The apparatus as claimed in any of the preceding Claims, c h a r a c t e r i z e d in that the electrodes (6,15,16,24) are coated with a layer (27) of porous material for accommodating therapeutic substances (28).

Fig. 1

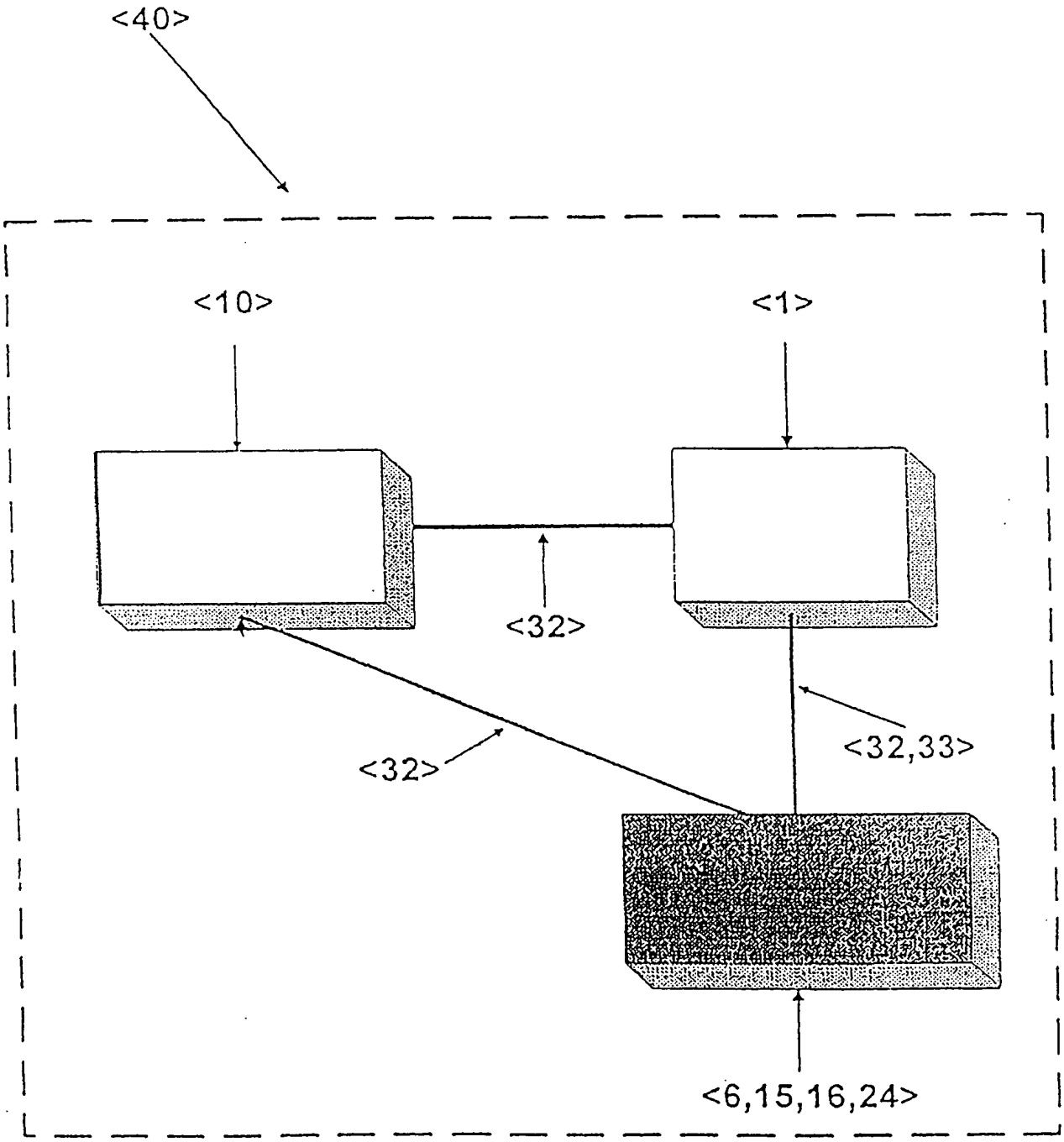


Fig. 2

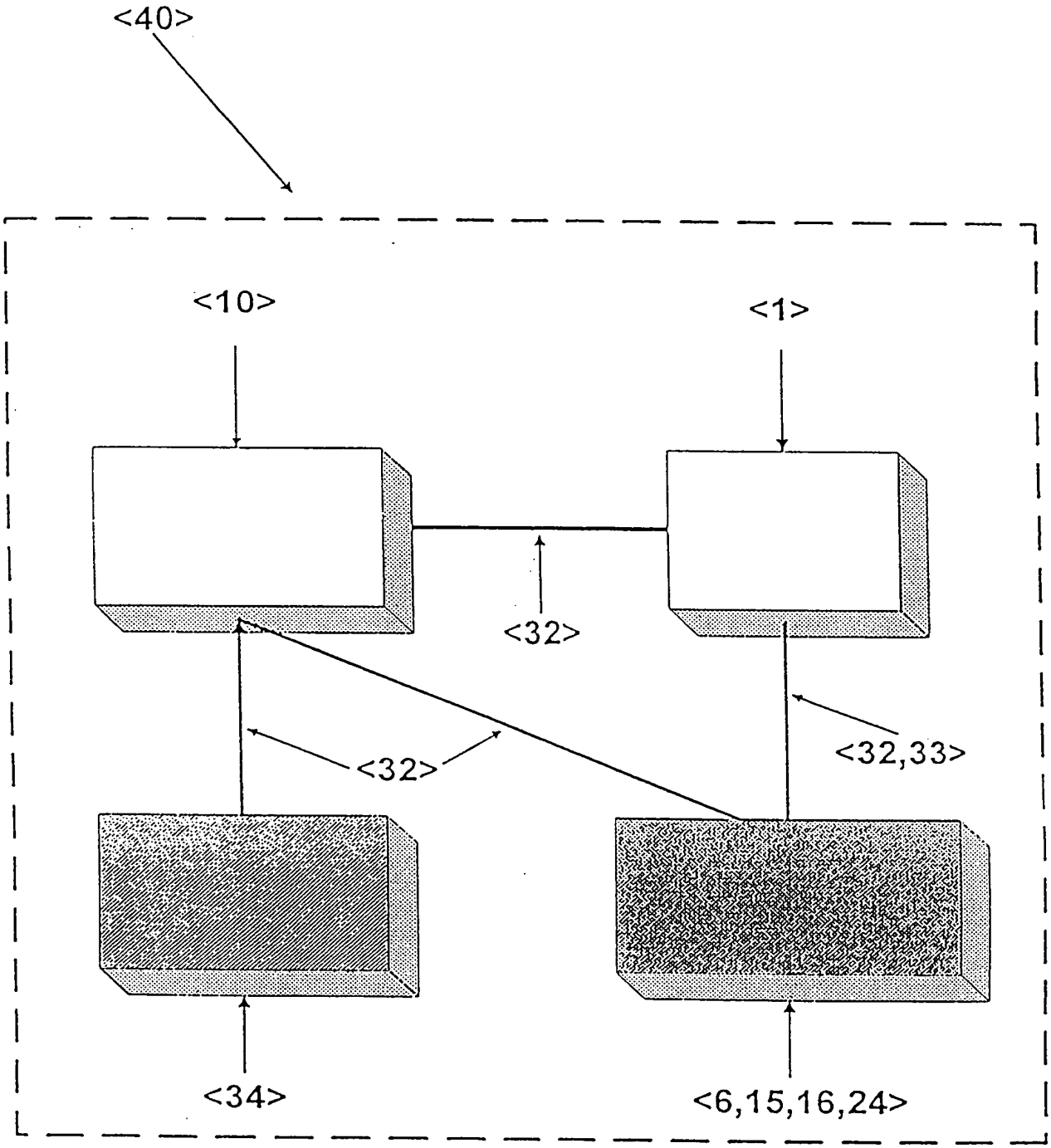


Fig. 3

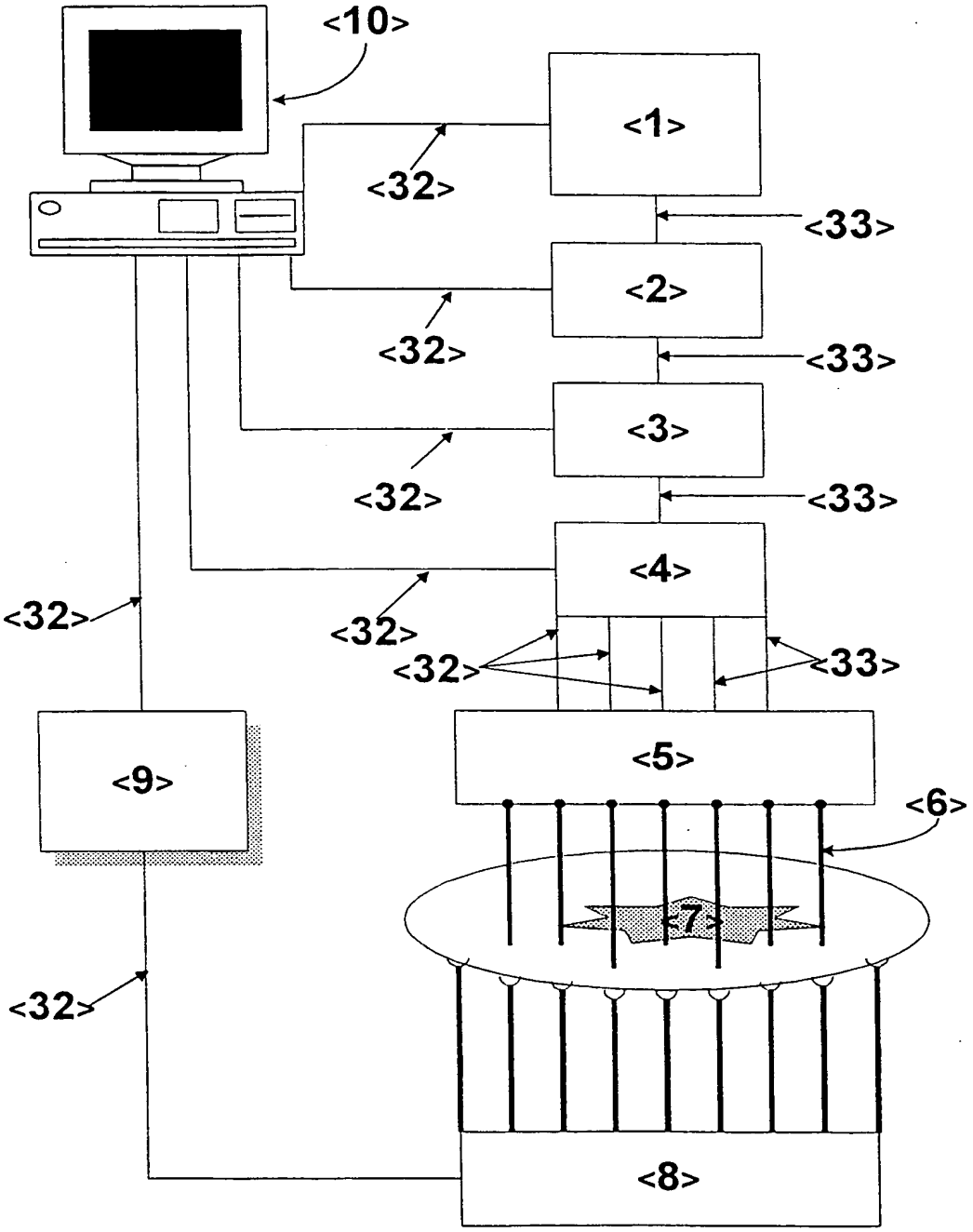


Fig. 4 a,b

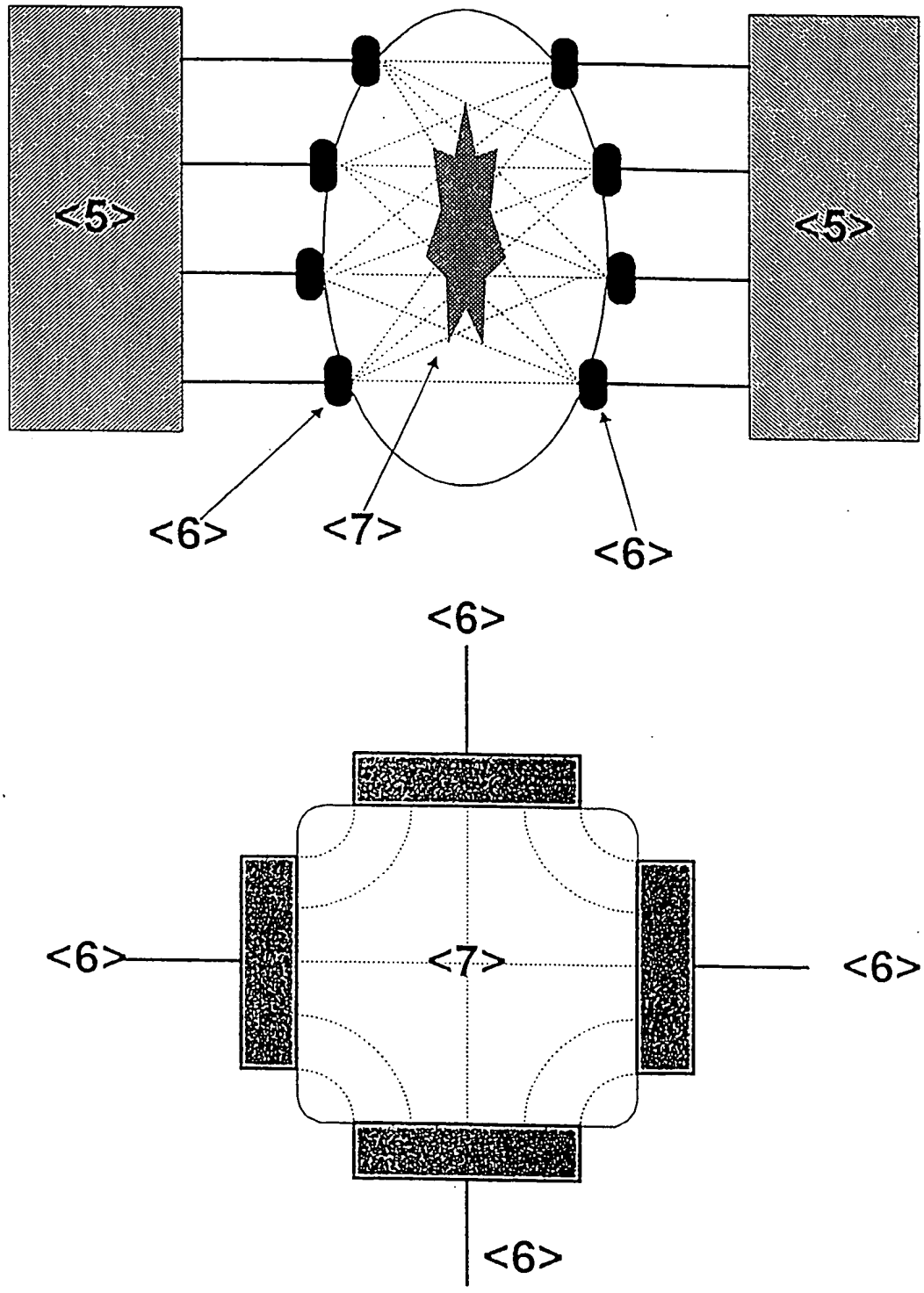


Fig. 4 c,d

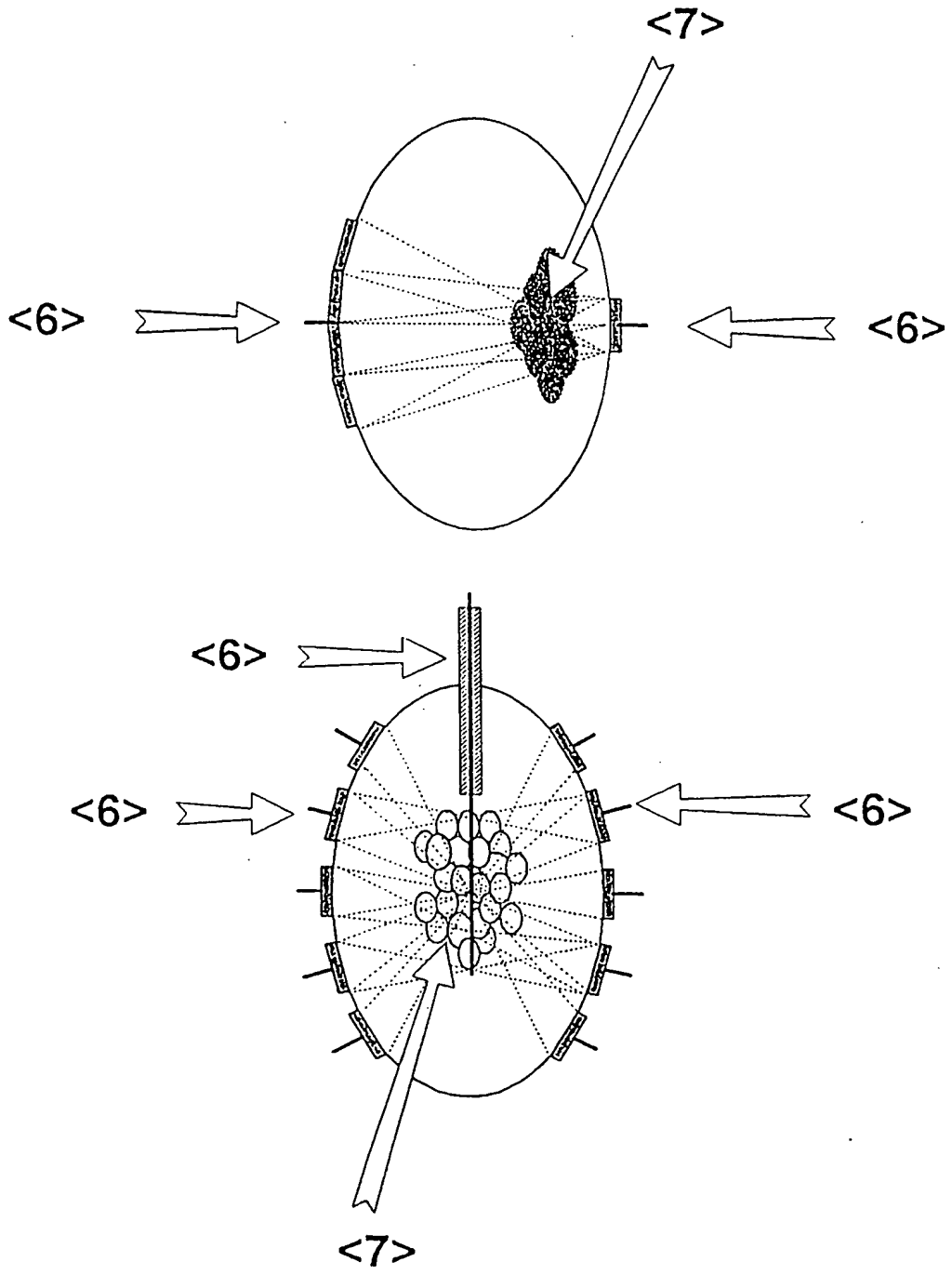
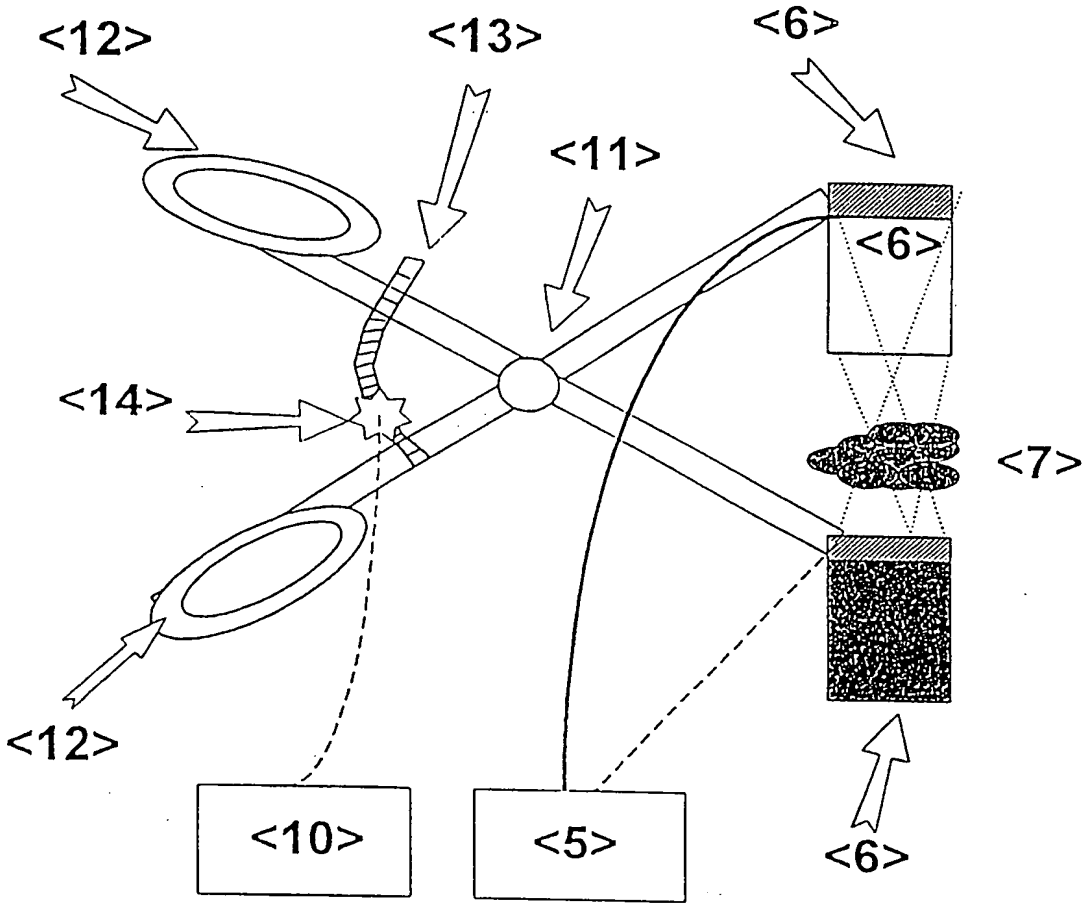


Fig. 5



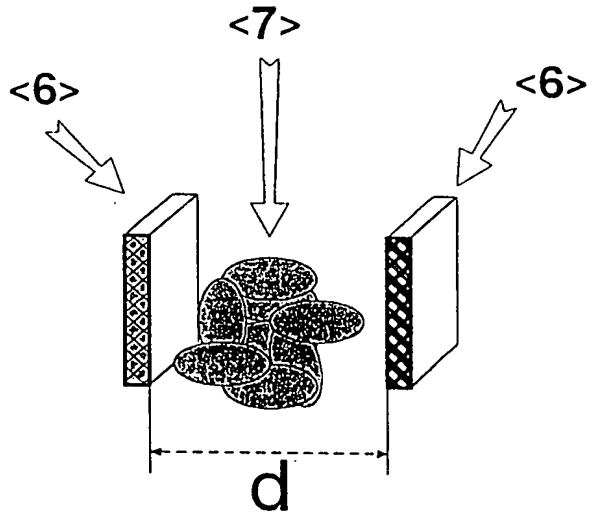


Fig. 6 a

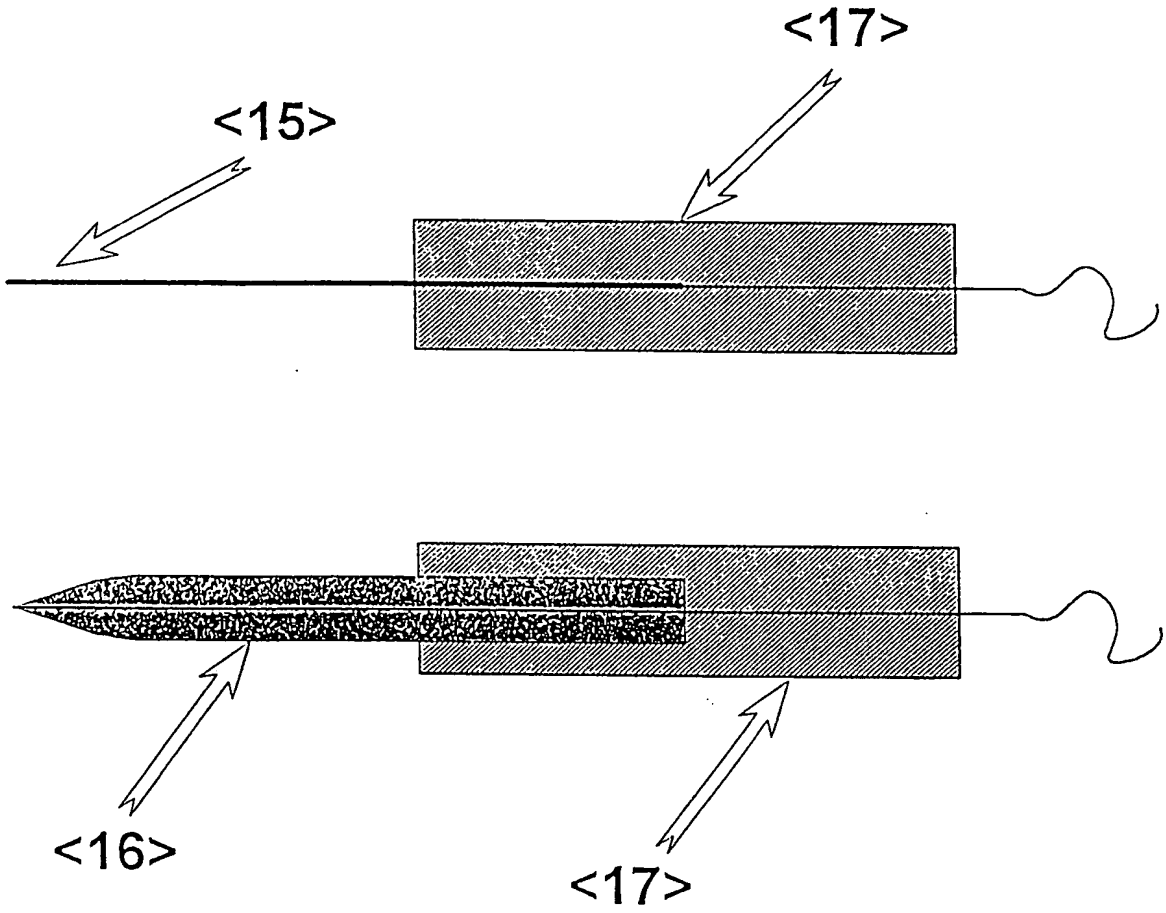


Fig. 6 b

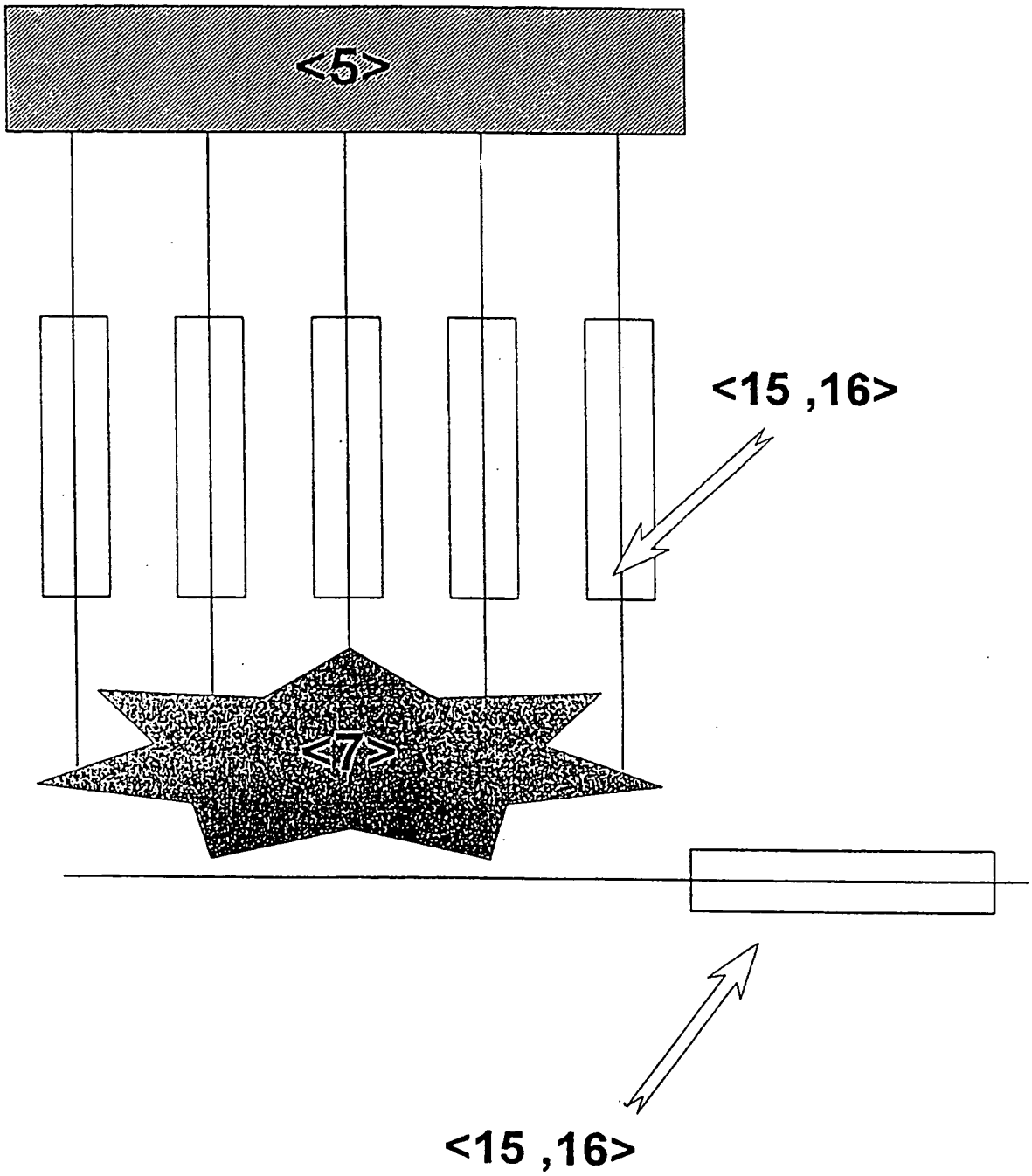


Fig. 6 c

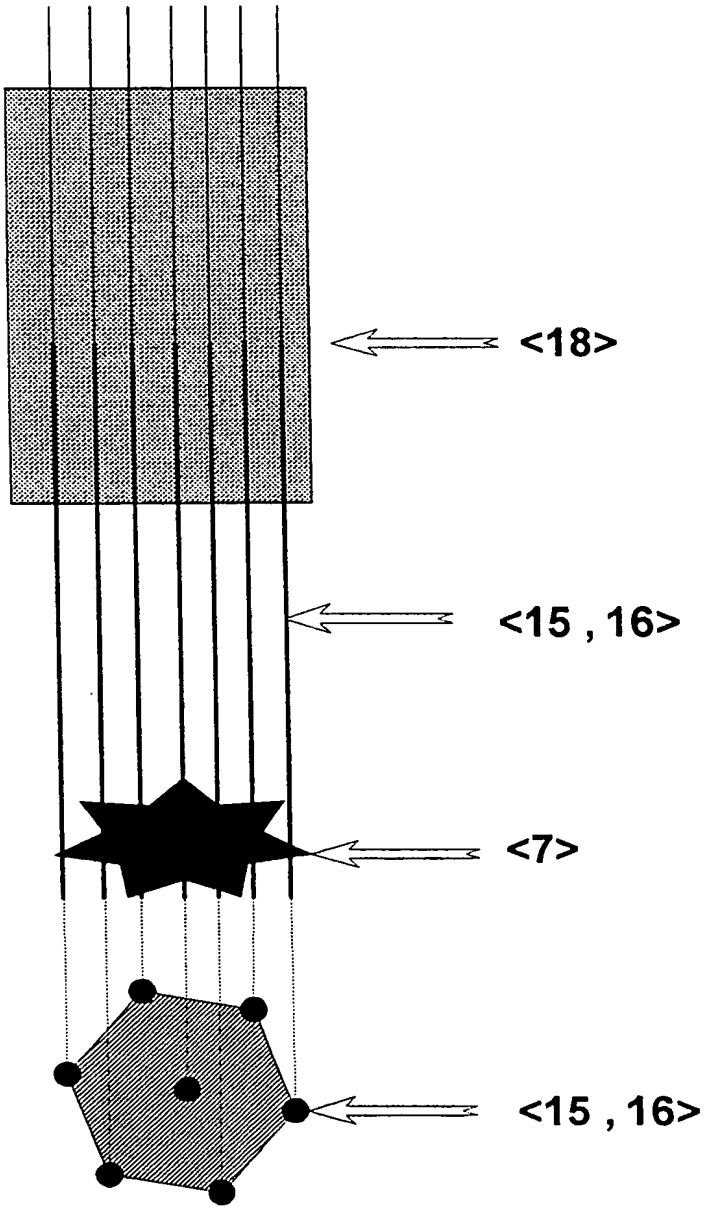


Fig. 6 d

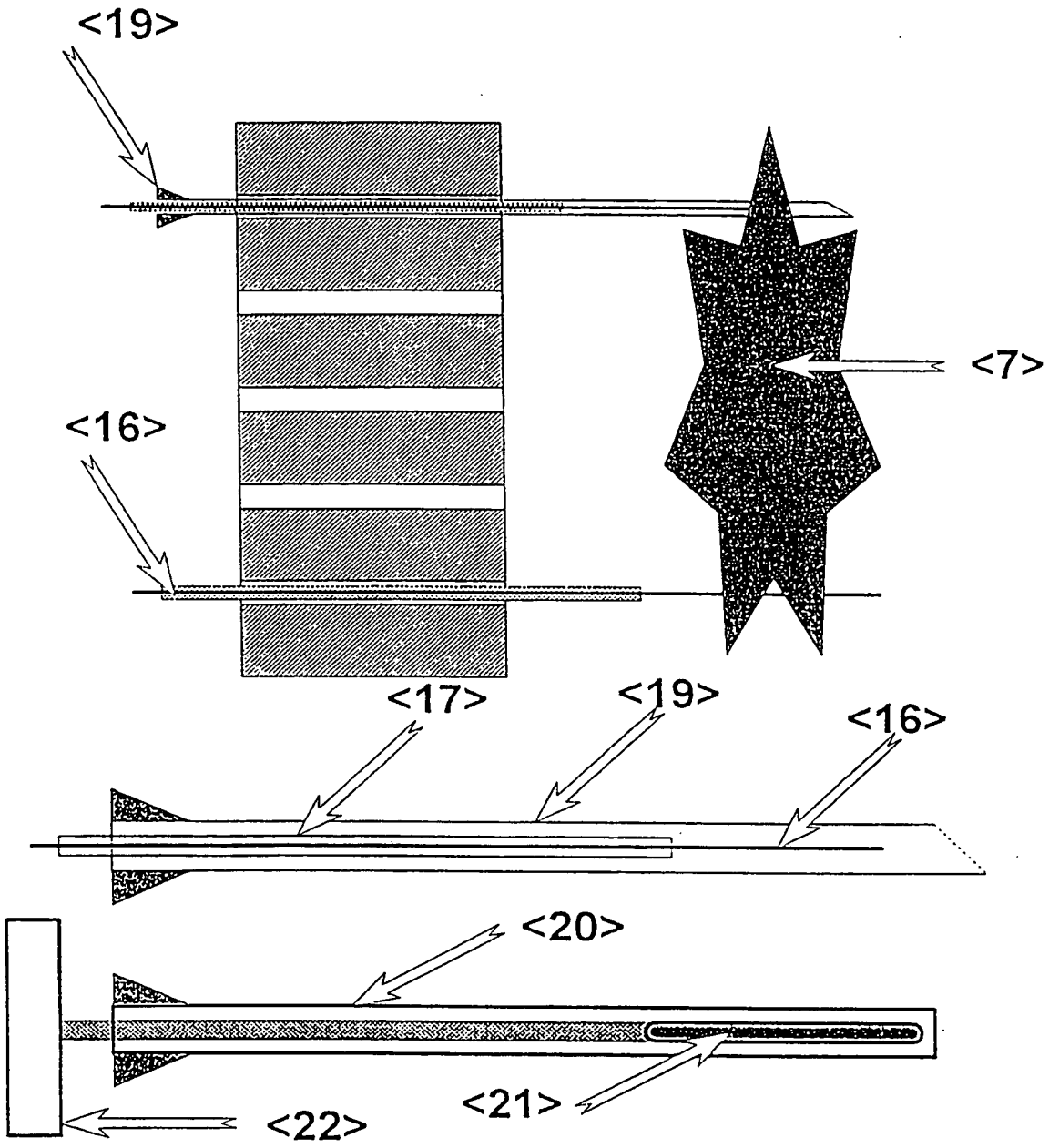


Fig.7 a-c

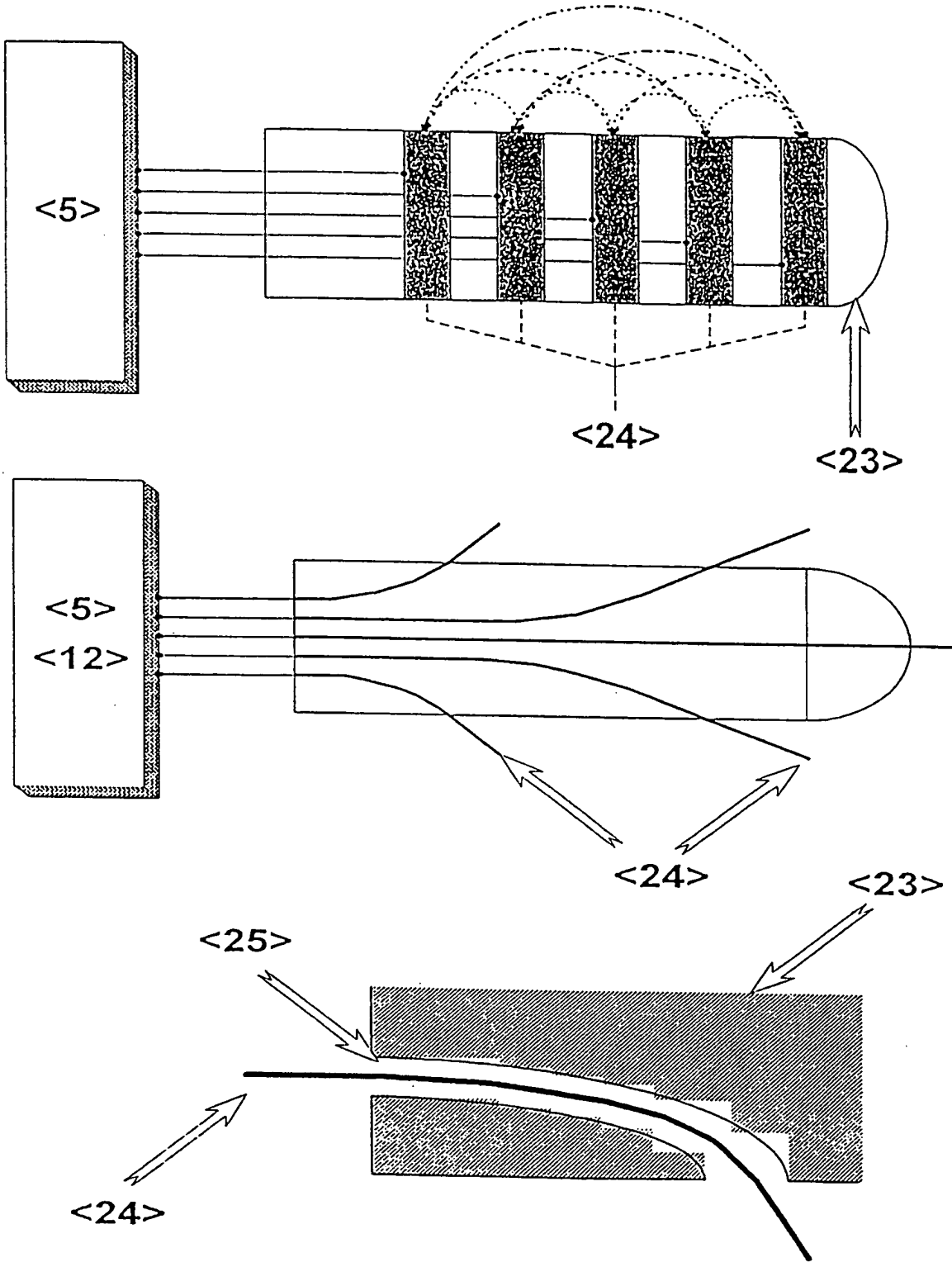


Fig. 8

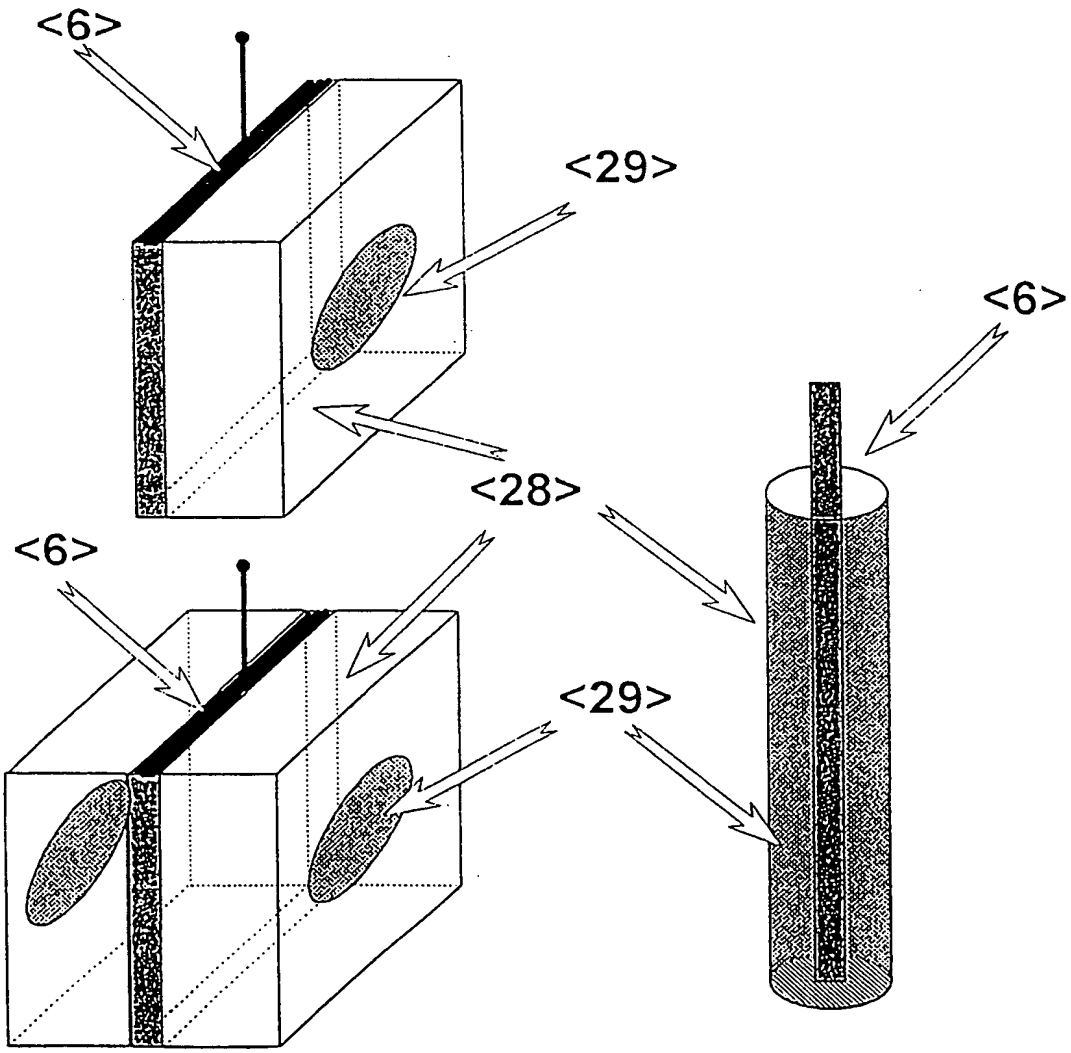


Fig. 9 a-e

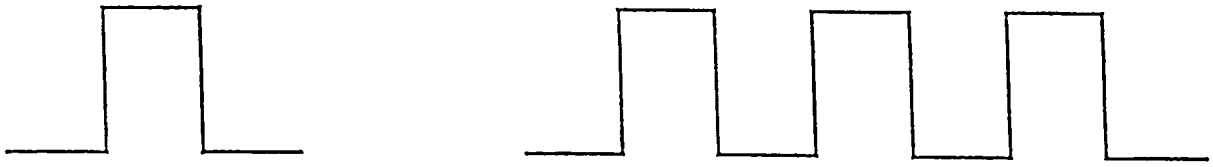


Fig. 9 a

Fig 9 b

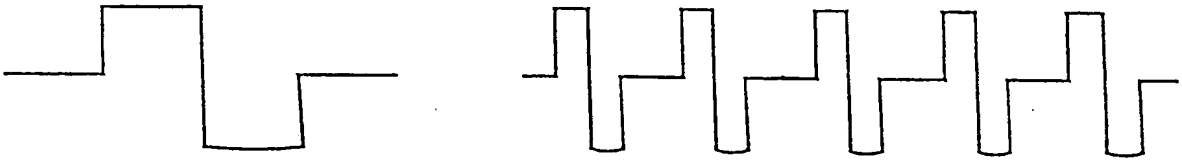


Fig 9 c

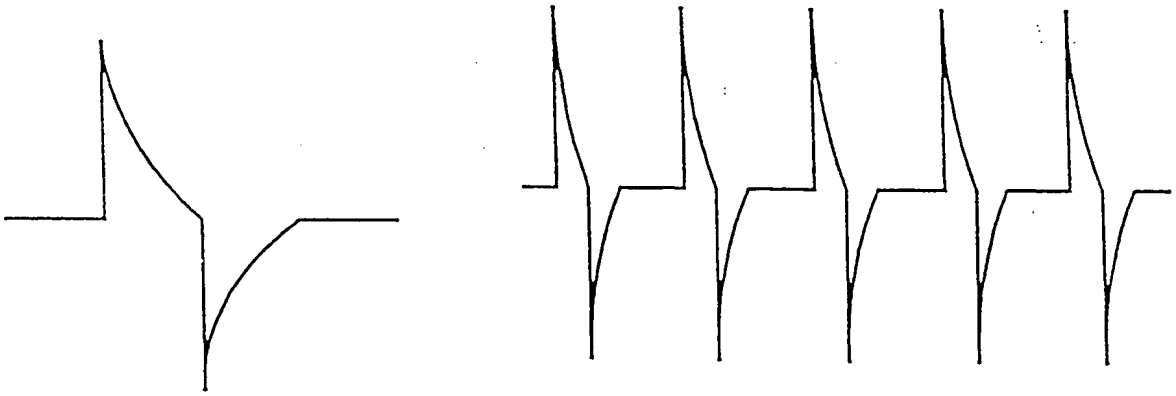


Fig. 9 d

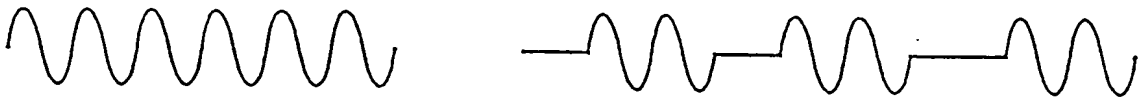


Fig 9 e

Fig. 10

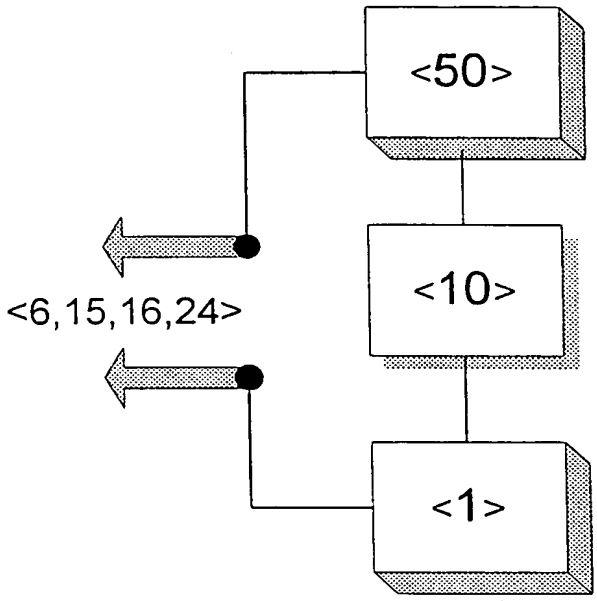


Fig. 11 a,b

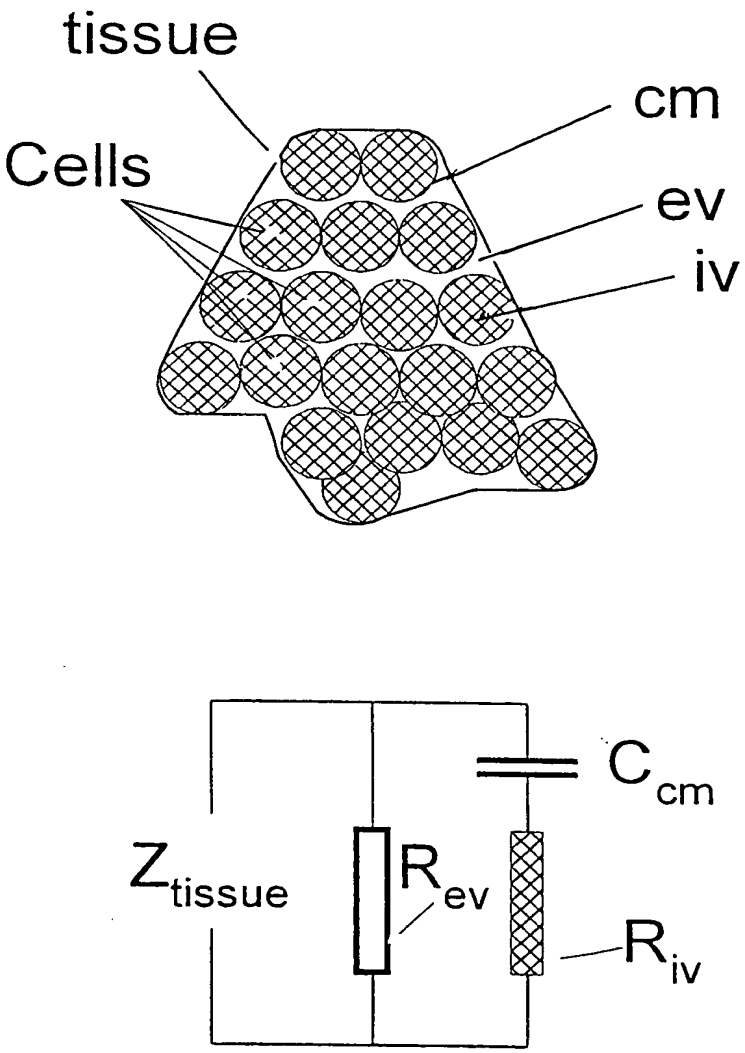
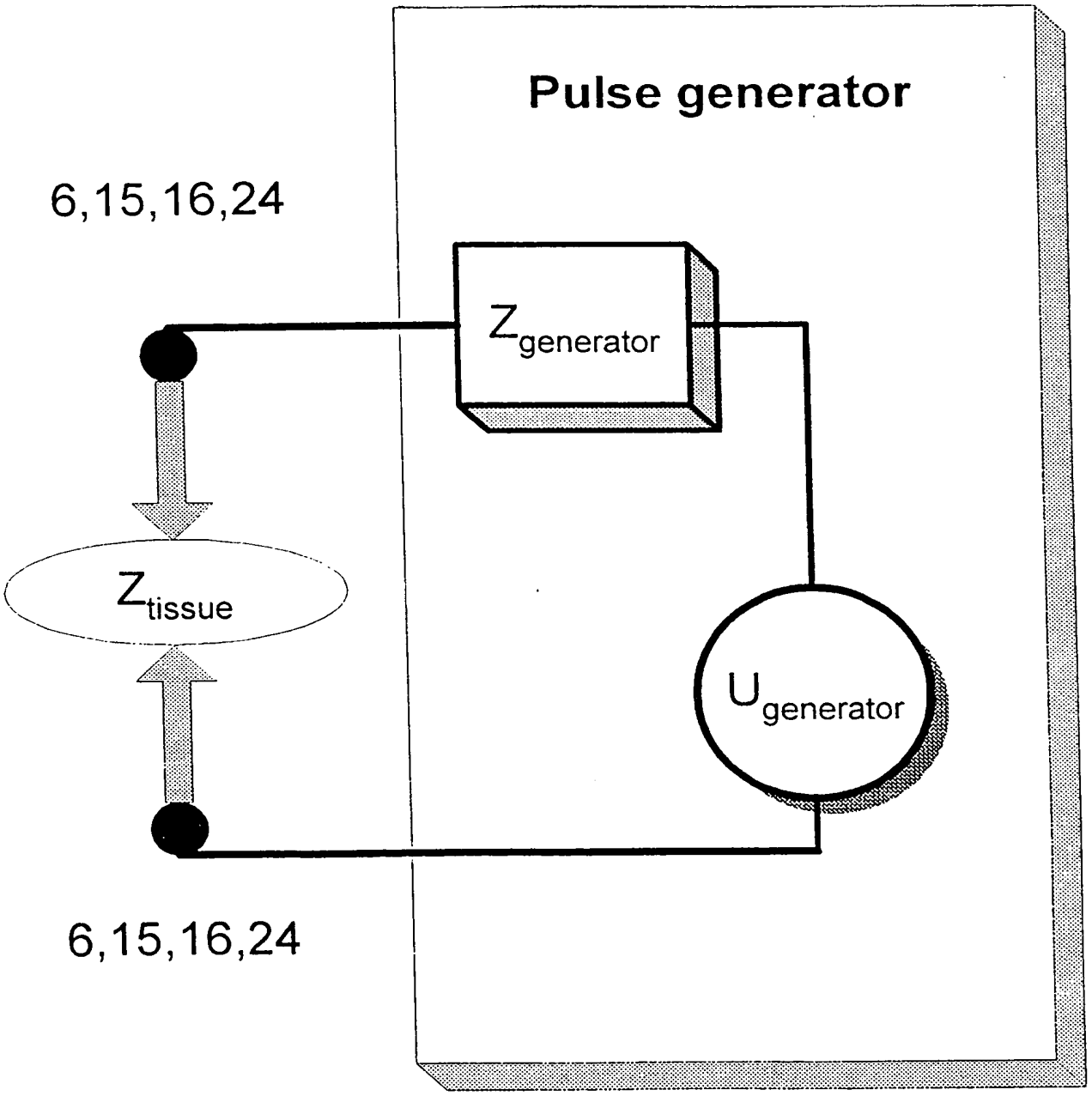


Fig. 12


Pulse generator
6,15,16,24
Z generator
Z tissue
U generator
6,15,16,24

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/00511

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61N 1/30, A61B 5/05
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61N, A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9707853 A1 (HISAMITSU PHARMACEUTICAL CO., INC.), 6 March 1997 (06.03.97), abstract	1-3,5-8, 16-18
Y		9-15
	--	
Y	WO 9323112 A1 (SCHOUENBORG, JENS), 25 November 1993 (25.11.93), page 15, line 32 - page 16, line 30, abstract	9,10
	--	
Y	US 5527357 A1 (G.E. SPRINGER, JR.), 18 June 1996 (18.06.96), column 2, line 38 - line 55	11-15
	--	

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 Sept 1999	14 -09- 1999
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. + 46 8 666 02 86	Authorized officer Lotta Gunnarsson/AE Telephone No. + 46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/00511

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4141359 A1 (S.C. JACOBSEN ET AL.), 27 February 1979 (27.02.79), column 3, line 45 - column 4, line 30 --	1-3,5-8
A	WO 9707854 A1 (BECTON DICKINSON AND COMPANY), 6 March 1997 (06.03.97), page 2, line 10 - page 4, line 10, abstract --	1-3,5-8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE99/00511

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **4**
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by surgery (Article 17(2)(a)(i), Rule 39.1 (iv)).

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1) Device to control the size of the pulse with impedance measurements. (Claims 1-3 and 5-8).

2) The shape of the electrodes that create the electrical field. (Claims 9-18).

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/SE 99/00511

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9707853 A1	06/03/97	AU 696832 B	17/09/98
		AU 6669996 A	19/03/97
		CA 2229872 A	06/03/97
		EP 0847775 A	17/06/98
		JP 9066111 A	11/03/97
		JP 9108362 A	28/04/97
WO 9323112 A1	25/11/93	AT 141177 T	15/08/96
		AU 4096193 A	13/12/93
		CA 2135301 A	25/11/93
		DE 69304035 D,T	19/12/96
		EP 0606412 A,B	20/07/94
		ES 2090999 T	16/10/96
		PL 171134 B	28/03/97
		SE 469465 B,C	12/07/93
		SE 9201453 A	12/07/93
		US 5449378 A	12/09/95
US 5527357 A1	18/06/96	AU 2909195 A	19/01/96
		WO 9600108 A	04/01/96
US 4141359 A1	27/02/79	US 4166457 A	04/09/79
WO 9707854 A1	06/03/97	AU 6962496 A	19/03/97
		CA 2230813 A	06/03/97
		EP 0847293 A	17/06/98